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Original article

Study of cardiac biomarkers in patients with acute coronary syndrome

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Abstract:

Introduction: This study was designed to study clinical profile of patients with Acute Coronary Syndrome and to correlate between onset of ACS and rise in different cardiac markers in patient of ACS during hospital stay. The basic assumption of this study was that the use of cardiac TnT and CK-MB may lead to a more accurate diagnostic and prognostic evaluation of ACSs, compared with the use of conventional enzyme activities. Moreover, acute-phase proteins and cytokines were assumed to have a prognostic significance beyond myocardial injury in ACSs.

Material and methodology: The present study was conducted in Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune. The college was established in 1996 and has 1290 bedded well equipped own hospital, backed by a Research Centre. The hospital mainly caters urban, peri urban and rural population living around Pimpri, Pune.This study was conducted among the patients coming to the Outpatient department/emergency department with the symptoms suggestive of Acute Coronary Syndrome (ACS).

Results: In the present study, the association between mean CK-MB level at admission and after 72 hrs of admission is statistically significant with p value 0.001. The association between the level of CK-MB in the patients who are alive and who died after the episodes of ACS is also statistically significant. ($p<0.001$).cTn typically increases more than 20 times above the upper limit of the reference range in myocardial infarction as compared to creatine kinase-myocardial band (CK-MB) which usually increases 10 times above the reference range.

Conclusion: From this study, we conclude, level of Serum Myoglobin was the earliest to rise in the cases of Acute Coronary Syndrome. Its level was within normal limits after 72 hours of admission. Troponin I and Troponin T remain positive in the cases even after 72 hours of admission. Mortality was seen is more in ST segment elevation MI and Non-ST segment elevation MI compared to Unstable angina.

Keywords: Acute coronary syndrome, biomarkers, myocardial infarction.

Introduction:

With the introduction of new more sensitive and cardiac-specific biochemical markers of myocardial injury, such as cardiac troponins T (TnT) and I (TnI), smaller myocardial injuries could be recognized. These injuries were primarily termed 'minimal myocardial damage' [(1)], and they were found to be associated with an adverse prognosis [(2)]. Thus, the adoption of these markers in modern clinical practice has led to a need for the redefinition of MI [(8)]. One major goal of this redefinition has been to integrate prognostic aspects with the diagnosis of Acute coronary syndromes (ACSs). However, the impact of the introduction of these markers instead of the conventional enzymes on the number of MI diagnoses and on the prognostic stratification of ACSs has not been clear.

In recent years, the role of inflammation in the pathogenesis and prognosis of CHD has been a subject of great interest [(3,4)]. The association of inflammation markers, first of all C-reactive protein (CRP), with the risk of future coronary events has been shown not only in patients with stable angina pectoris or UAP [(5)], but also in apparently healthy persons [(6)]. However, the mechanisms of these associations are incompletely understood. Inflammation markers such as CRP have been found to give information both on inflammatory activity (the underlying condition) and on myocardial cell injury (the acute event).

This study was designed to study clinical profile of patients with Acute Coronary Syndrome and to correlate between onset of ACS and rise in different cardiac markers in patient of ACS during hospital stay. The basic assumption of this study was that the use of cardiac TnT and CK-MB may lead to a more accurate diagnostic and prognostic evaluation of ACSs, compared with the use of conventional enzyme activities. Moreover, acute-phase proteins and cytokines were assumed to have a prognostic significance beyond myocardial injury in ACSs.

Material and methodology:

The present study was conducted in Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pimpri, Pune. The college was established in 1996 and has 1290 bedded well equipped own hospital, backed by a Research Centre. The hospital mainly caters urban, peri urban and rural population living around Pimpri, Pune.

This study was conducted among the patients coming to the Outpatient department/emergency department with the symptoms suggestive of Acute Coronary Syndrome (ACS).

The "Study of Cardiac Biomarkers in Patients Presenting with Acute Coronary Syndrome" is a descriptive longitudinal study. The selected eligible patients are contacted once at the time of admission in the hospital and second examination was done after 72 hrs of admission. All required information, examination and investigations were carried out once at the time of admission and other after 72 hrs of admission. Only the outcome of the cases i.e. whether the case is alive or died is noted up to 30 days after the episode of ACS.

Considering the frequency of the patients coming with the symptom of ACS and the study duration it was decided to take approximately sixty cases of ACS in the study. Considering the study objectives it was found that patients attending Outdoor Patient Department (OPD) of General Medicine, emergency department and medicine ward were recruited as study subjects. So study subjects were selected from

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the patients attending Medicine department and fulfilling the inclusion and exclusion criteria.

The study participants were enrolled consecutively in the study until the desired sample size was achieved. Each day one or two subjects were enrolled in the study. Considering the rareness and lower frequency of cases, we decided to enroll the cases consecutively. Those patients or whose first blood relatives denied to take part in the study were excluded from the study.

Both the genders were included in the study.

Patients coming to the institute with the symptoms of Acute Coronary Syndrome. The inclusion criteria were:

1. All patients of Acute coronary syndrome.
2. All patients presenting chest pain more than 3 hours.

As the study tries to find out clinical and biochemical changes in the cardiac markers related to Acute Coronary Syndrome, known disease or pre-existing disease which can alter the level of cardiac markers are excluded from the study. This exclusion list includes , acute pulmonary embolism , stroke , sepsis , COPD , ESRD , myocarditis , pericarditis , connective tissue disorders etc.

After selection of eligible patients a predesigned questionnaire was used to record patients' data. Data management and analysis was done using Microsoft excel and Epi-info software.

Results:

There were 60 cases of Acute Coronary Syndrome involved in the study. The mean age of participants was 54.28 ± 12.515 years. It is inferred from the above that 66.7% of the participants were male while 33.3% of the participants were female. Regarding clinical symptoms it is seen that all the cases were suffering from chest pain. Chest pain is one of most clinical symptom in the cases of Acute Coronary Syndrome. Dyspnoea was observed in the 66.7% of the participants out of the total 60 cases. There were 33.3% of the cases who were not having dyspnoea at the time of admission. Nausea/Vomiting was present in 38.3% of the participants at the time of admission of the cases. The mean duration of symptoms was 10.15 ± 13.144 hrs. Duration of symptoms of Acute Coronary syndrome was 3-6 hrs in 66.1% of the cases. It was seen that 11.9% of the cases had duration of 7-9hrs, 8.5% had 10-12 hrs of symptoms.It was seen that 56.7% of the cases were having the past history of hypertension at the time of admission in the hospital. Diabetes was present in 61.7 of the cases at the time of admission in the hospital due to ACS.Past history of Ischemic Heart Disease were present in 51.7% of the cases at the time of admission in the hospital due to ACS.It is seen that presence of smoking abuse was seen in 41.7% of the cases while alcohol abuse was present in 41.7% of the cases. Obesity was present in 13.3% of the cases. Dyslipidaemia was present in 43.3% of the cases. Mortality was present in 20% of the cases.

In our study, Troponin I was positive in 70% of the cases at the time of admission in hospital due to ACS. Troponin T was positive in 66.7% of the cases at the time of admission in hospital due to ACS. Troponin I was positive in 66.7% of the cases after 72 hrs of admission in hospital due to ACS. Troponin T was positive in 66.7% of the cases after 72 hrs of admission in hospital due to ACS.

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Table 1: Comparison of level of Sr. Myoglobin, CK-MB, HsCRP on admission and after 72 hrs

Variable	N	Mean	Std. deviation
On admission Sr. Myoglobin	60	115.73	61.564
After 72 hrs Sr. Myoglobin	56	44.32	21.269
On admission CK-MB	60	44.12	24.964
After 72 hrs CK-MB	56	13.95	6.518
On admission hsCRP	60	2.12	1.821
After 72 hrs hsCRP	56	0.63	0.622
Ejection Fraction	60	50.08	9.544

It seen from the above table that on admission the Sr. Myoglobin level was 115.73 (SD 61.54) while after 72 hrs it was 44.32 (SD 21.269). Similarly, it was observed that on admission the CK-MB level was 44.12 (SD 24.96) while after 72 hrs it was 13.95 (SD 6.518) and on admission HsCRP level was 2.12 (SD 1.821) while after 72 hrs it was 0.63 (SD 0.622). The mean ejection fraction of the participants was 50.08 (SD 9.544)

Among the 60 cases who participated in the study, 41.7% were diagnosed as ST segment elevation Myocardial Infarction, 30.0% were diagnosed as Unstable Angina and 28.3% were diagnosed as Non ST segment Elevation Myocardial Infarction.

Table 2: Association between Serum Myoglobin level on admission and after 72 hrs of admission

Variable	Sample size	Mean	Std. Dev.	p-value
On admission Sr. Myoglobin	60	115.73	61.56	0.001
After 72 hrs Sr. Myoglobin	56	44.32	21.26	

The association between mean Sr. Myoglobin level at admission and after 72 hrs of admission is statistically significant with p value 0.001.

Table 3: Association between CK-MB level on admission and after 72 hrs of admission

Variable	Sample size	Mean	Std. Dev.	p-value
On admission CK-MB	60	44.12	24.96	0.001
After 72 hrs CK-MB	56	13.95	6.51	

The association between mean CK-MB level at admission and after 72 hrs of admission is statistically significant with p value 0.001.

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Table 4: Mean and SD of Cardiac markers in relation to diagnosis

Diagnosis		**On Admission Sr. Myoglobin**	**After 72 hrs Sr. Myoglobin**	**On Admission CK-MB**	**After 72 hrs CK-MB**
NSTEMI	Mean	42.75	120.47	54.53	16.13
	N	16	17	17	16
	SD	22.884	38.978	19.953	8.570
STEMI	Mean	51.09	155.00	54.08	13.61
	N	23	25	25	23
	SD	23.737	53.547	22.531	5.492
UA	Mean	36.65	56.72	20.44	12.35
	N	17	18	18	17
	SD	12.589	41.221	14.960	5.303
Total	Mean	44.32	115.73	44.12	13.95
	N	56	60	60	56
	SD	21.269	61.564	24.964	6.518

Table 5: Mean and SD of hsCRP, Age and duration of symptom in relation to diagnosis

Diagnosis		On Admission hsCRP	After 72 hrs hsCRP	Age	Duration of Symptom (hrs)
NSTEMI	Mean	2.05	0.61	52.94	12.65
	N	17	16	17	17
	SD	2.092	0.572	13.571	18.507
STEMI	Mean	2.59	0.80	57.52	8.76
	N	25	23	25	25
	SD	1.695	0.713	12.774	9.107
UA	Mean	1.54	0.42	51.06	9.72
	N	18	17	18	18
	SD	1.628	0.481	10.563	12.285
Total	Mean	2.12	0.63	54.28	10.15
	N	60	56	60	60
	SD	1.821	0.622	12.515	13.144

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Mean S. Myoglobin level was highest in STEMI while mean CK-MB was almost equal in STEMI and NSTEMI. Mean HsCRP level was comparable with all the diagnosis but it was found lower in Unstable angina. After 72 hrs of admission, mean Myoglobin level, mean CKMB level and mean hsCRP level was within the normal limits. The mean age was higher in STEMI as compared to other diagnosis.

Table 6: Cross tabulation showing diagnosis with respect to presence of Diabetes

Diabetes		Diagnosis			Total
		NSTEMI	STEMI	UA	
Present	Count	5	12	6	23
	% within Diagnosis	29.4%	48.0%	33.3%	38.3%
Absent	Count	12	13	12	37
	% within Diagnosis	70.6%	52.0%	66.7%	61.7%
Total	Count	17	25	18	60
	% within Diagnosis	100.0%	100.0%	100.0%	100.0%

It is seen that among the NSTEMI diabetes was absent in 70.6% of the cases while in STEMI diabetes was absent in 52.0% cases. Diabetes was present in only 33.3% of the cases.

Table 7: Association of mortality with respect to level of Cardiac markers on Admission and after 72hrs of admission

Cardiac Markers	Mortality	N	Mean	Std. Deviation	P value
On admission Sr. Myoglobin	Death	12	151.75	56.705	0.02
	Alive	48	106.73	59.928	
On admission CK-MB	Death	12	70.83	21.040	0.001
	Alive	48	37.44	21.235	
On admission hsCRP	Death	12	4.13	1.965	0.001
	Alive	48	1.62	1.405	
After 72 hrs Sr. Myoglobin	Death	8	71.63	21.314	0.001
	Alive	48	39.77	17.711	
After 72 hrs CK-MB	Death	8	16.25	3.105	0.08
	Alive	48	13.56	6.872	
After 72 hrs hsCRP	Death	8	1.74	0.527	0.001
	Alive	48	0.45	0.407	

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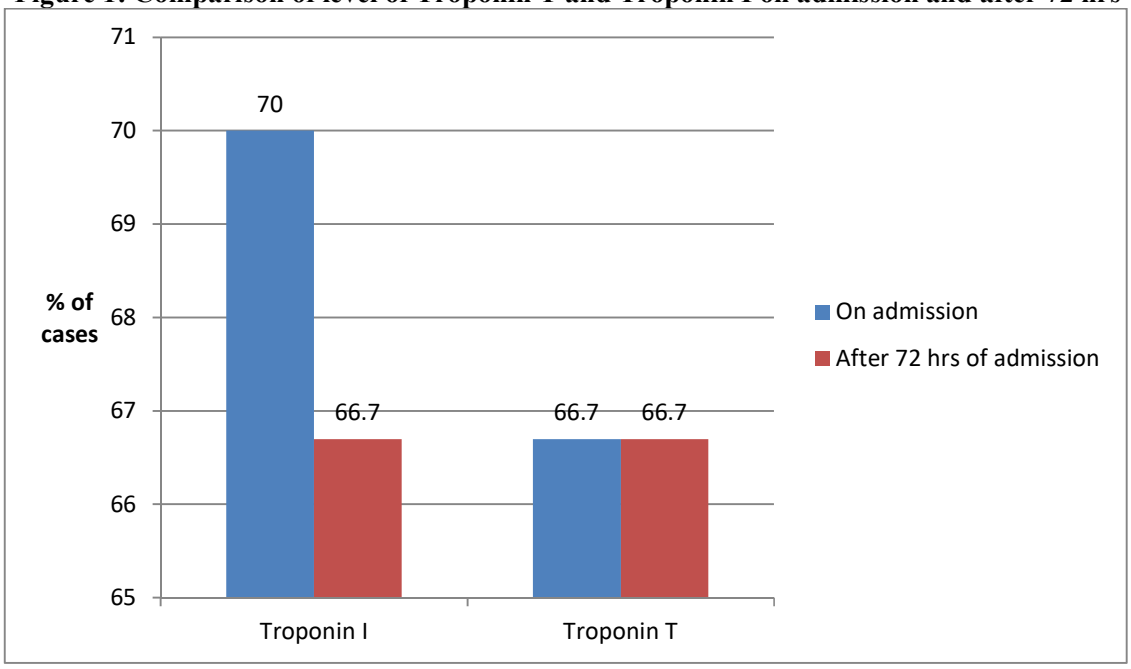
Figure 1: Comparison of level of Troponin T and Troponin I on admission and after 72 hrs



Discussion:

In the present study, the association between mean CK-MB level at admission and after 72 hrs of admission is statistically significant with p value 0.001. The association between the level of CK-MB in the patients who are alive and who died after the episodes of ACS is also statistically significant. ($p<0.001$).cTn typically increases more than 20 times above the upper limit of the reference range in myocardial infarction as compared to creatine kinase-myocardial band (CK-MB) which usually increases 10 times above the reference range. This provides an improved signal - to - noise ratio, enabling the detection of even minor degree of necrosis with troponin. The cTn begins to elevate 3 h from the onset of chest pain in MI. Because of the continuous release, cTn elevation persists for days (cTnI: 7-10 days, cTnT: 10-14 days). This prolonged course of release with troponin is advantageous for the late diagnosis of MI, however, it limits the diagnosis of early re-infarction.

In the present study, Troponin I was positive in 88.2% of NSTEMI and 100% STEMI cases while it was negative in 88.9% cases of Unstable Angina. In the present study, Troponin T was positive in 88.2% of NSTEMI and 100% STEMI cases while it was negative in 100% cases of Unstable Angina. In the present study after 72 hours of admission, Troponin I was positive in 94.1% cases of NSTEMI, 92% cases of STEMI and it was negative in 88.9% cases of unstable angina. Similarly in our study after 72 hours of admission, Troponin T was positive in 94.0% cases of NSTEMI, 92% cases of STEMI and it was negative in 88.9% cases of unstable angina.

The effect of TnT or TnI on the MI diagnosis rate was also studied in a series of 3420 patients enrolled in the Global Registry of Acute Coronary Events in 94 centres in 15 countries [(7)]. An isolated elevation of

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troponin concentration as the criterion for MI increased the number of MI diagnoses by 15%, 26%, and 9%, compared to the diagnoses based on CK the URL, CK > two times the URL, and CK-MB the URL, respectively. Moreover, among the patients with CK - two times the URL, the troponin positive patients had 3-fold higher in-hospital mortality than those with cardiac troponin within normal limits [7]. Among the patients with CK > two times the URL, the in-hospital mortality was 1.5-fold higher in the troponin positive patients compared with those without elevated cardiac troponin. In another sub study of the Global Registry of Acute Coronary Events, the in-hospital risk of death or recurrent MI was 3-fold higher in patients with non-ST-elevation MI based on isolated troponin elevation than in patients with TnT or TnI within normal limits [8]. The risk was 2-fold higher in patients with non-ST-elevation MI with both elevated CK-MB (or CK) and cardiac troponin than in those with isolated troponin elevation, respectively. There was no difference in the likelihood of re-vascularisation between the two non-ST-elevation MI groups. In a study based on a German Acute Coronary Syndromes registry [9], the new definition increased the number of non-ST-elevation MIs by as much as 124% compared with patients with elevated CK levels and no ST-segment elevation. In-hospital mortality was 2-fold higher in patients with elevated CK levels than in patients with isolated troponin elevation. In a study by Trevelyan *et al.* [10] the 6-month prognosis with regard to major adverse cardiovascular events was similar in patients with elevated TnT, regardless of the diagnosis by the WHO criteria. The patients with TnT within normal limits had a superior prognosis, but they were not event-free. Wilson *et al.* [11] found that in-hospital mortality fell from 7.4% to 4.6% when the diagnosis of MI was based on TnT or TnI instead of CK >400 U/l. Correspondingly, Large *et al*. [12] found that in-hospital case fatality fell from 12.8% to 7.1% when the ESC/ACC criteria were used instead of "traditional criteria". Finally, in the study by Aguiar *et al.* [13] among patients with non-ST-elevation ACSs, 30-day outcome was similar in patients with elevation of CK-MB to those with isolated elevation of TnI.

The inclusion of cardiac troponins in the diagnostic criteria of MI leads to an increase in the number of MI diagnoses. The magnitude of this increase is strongly dependent on which criteria, *e.g.*, enzymes and their cut-off values, are used in the conventional diagnosis of MI, since the definition of MI has varied in different studies. The increase in the number of MIs with the introduction of more sensitive and specific diagnostic methods is not a new phenomenon in the evolution of MI diagnosis. It was demonstrated already in the 1980s in the Minnesota Heart Survey that the attack rate of MI increased by 17% or 24% when CK or CK- MB activities were added to the diagnostic algorithm [14].

In the present study, the change in the Sr. Myoglobin, CK-MB level and HsCRP level on admission was found to be statistically significant with p value less than 0.001. C-reactive protein is a nonspecific inflammatory marker that is released by the liver in response to the acute phase injury. CRP can be measured by multiple assays in acceptable precisions down to or below 0.3 mg/l and most give comparable results (designated as high-sensitive CRP or hsCRP). CRP in addition to BNP and troponin does appear to provide some additional value in the prognostication of ACS; however, the incremental value is modest. In terms of the association of CRP and ACS it is important to distinguish cases without (unstable

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angina) and with necrosis (acute MI). In cases of AMI, CRP release is triggered as an acute phase reactant secondary to necrosis and levels of CRP are much higher and these have been correlated with infarct size. Though infarct size is the major determinant of long term prognosis after AMI; mortality has been shown to be related to CRP levels independent of left ventricular systolic function [(15)]. In the absence of infarction, CRP levels correlate to the extent of atherosclerosis and some studies have shown that it predicts coronary events in patients of unstable angina independent of troponin levels [(16)]. However, a more recent large prospective study showed only a weak association of CRP levels and future coronary events in patients of ACS and even this disappeared once adjusted for other common clinical variables. This study included about two-thirds of AMI patients and one-third unstable angina patients [(17)].

Another interesting implication of CRP in ACS has been in terms of treatment: in a study of ACS patients, those with low CRP levels after statin therapy had better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol. Thus implying that statin therapy in these high risk patients of ACS should be driven not only by the target lipid levels but also the CRP levels achieved [(14)] These data suggest that CRP levels in ACS may be of prognostic significance but their incremental value over conventional factors and biomarkers may be modest.

Conclusion:

From this study, we conclude, level of Serum Myoglobin was the earliest to rise in the cases of Acute Coronary Syndrome. Its level was within normal limits after 72 hours of admission. Troponin I and Troponin T remain positive in the cases even after 72 hours of admission. Mortality was seen is more in ST segment elevation MI and Non-ST segment elevation MI compared to Unstable angina.

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