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A STUDY OF SERUM PRO-CALCITONIN LEVELS AS A PROGNOSTIC MARKER IN PATIENTS ADMITTED WITH ST ELEVATION MYOCARDIAL INFARCTION

General Medicine

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ABSTRACT

BACKGROUND- Acute myocardial infarction (AMI) remains a major cause of morbidity and mortality worldwide. Initial evidence suggests that Procalcitonin (PCT) can act as a potential blood based biomarker in AMI. Therefore, it may be helpful in prognostication and risk-stratification of patients with ST elevation myocardial infarction (STEMI) and help us to predict the risk of cardiovascular complications and outcome.
AIM- To study the association of PCT levels at the time of admission with incidence of cardiovascular complications in terms of cardiogenic shock, heart failure, arrhythmia and death in patients admitted with STEMI.
METHOD- A prospective observational study was conducted in a tertiary care centre of India. Patients diagnosed with STEMI were enrolled in the study after making the necessary exclusions. The PCT levels were checked at the time of admission along with electrocardiography (ECG), Echocardiography, Troponin I ,total leukocyte count (TLC), blood urea, creatinine and liver function test (LFT). Patients were followed till discharge / death and outcomes were recorded.
RESULT- Two hundred and fifty patients were included in the study (57.60 % males, mean age- 59.77±13.63 years). High PCT levels (>0.10 ng/ml) were significantly associated with cardiovascular complications in terms of cardiogenic shock, arrhythmia's, heart failure and significant left ventricular dysfunction. Raised PCT level was found to be a good predictor of mortality (relative risk =10.51).
CONCLUSION- Raised PCT levels were associated with higher cardiovascular complications and mortality in patients with STEMI. PCT levels at the time of admission may be useful as a biomarker in prognostication and risk stratification of STEMI patients.

KEYWORDS

Procalcitonin, ST elevation myocardial infarction, Acute coronary syndrome, Prognostic marker, Cardiovascular complications, Left ventricular dysfunction

INTRODUCTION-

Acute myocardial infarction (AMI) is a major cause of mortality and morbidity. It is responsible for over 15% of mortality every year worldwide.(1) India has also seen a progressive rise in the prevalence of coronary artery disease in the recent decades, both in urban (from 1% to 9-10%) as well as rural populations (from <1% to 4-6%).(2) AMI often results in serious complications including cardiac arrhythmia, heart failure and death. Early recognition of AMI is crucial to initiate appropriate treatment.

While the traditional methods of diagnosis include 12 lead ECG and cardiac biomarkers like troponin and creatine kinase, there has been expanding research into novel techniques. A multitude of blood-based biomarkers such as Heart fatty acid binding protein (Hfabp), glycogen phosphorylase isoenzyme BB, Ischemia-modified albumin, S100A from calcium-binding proteins, choline, Pregnancy- associated plasma protein A (PAPP-A), C Reactive protein (CRP), Tumor necrosis factor (TNF), Interleukin 6 (IL-6) and Interleukin-18 (IL-18) are being evaluated for their diagnostic and / or prognostic role. (3-10)

Serum procalcitonin (PCT) is a 116-amino acid peptide with a molecular weight of 14.5 kDa. Production is activated in all parenchymal tissues in response to cytokines, IL-6, TNF-α and IL-β.(11) Serum PCT concentration in healthy individuals is typically <0.10 ng/ml. A myriad of local and systemic insults (bacterial, fungal and malarial infections, major surgery, trauma, thermal injury, prolonged cardiogenic shock, malignancies and even certain drugs) can result in the elevation of serum PCT. PCT is detectable in blood within 3 to 4 hours following the triggering event, peaks at 6 to 12 hours and has a half-life of about 24 hours. Although traditionally utilized as a biomarker of sepsis, PCT is increasingly being utilized as a potential biomarker (diagnostic and prognostic) in a multitude of non-infective settings including acute mesenteric ischemia, congestive cardiac failure, cardiac arrest, febrile neutropenia, generalized pustular psoriasis, acute pancreatitis and gestational diabetes mellitus to name a few. (11-12, 13-16)

Serum PCT has also shown initial promise in predicting the prognosis of patients with AMI. Study done by Patel et al demonstrated that in patients of STEMI, high PCT level at 24 hours is significantly associated with no-reflow, cardiogenic shock as well as in-hospital and 30-days mortality.(17) Studies by HE Ataoglu et al and Kelly et al have also shown that higher PCT levels are associated with poor cardiovascular outcomes (18,19) However, further studies are needed to elaborate its role before it can be utilized as a standard of care in the management of AMI.

Hence, this prospective observational study was planned to evaluate the association of PCT levels with incidence of cardiovascular complication in terms of cardiogenic shock, heart failure, arrhythmia and death in patients admitted with STEMI and to assess its efficacy as a prognostic tool and thereby to aid in approach considerations for AMI management.

MATERIALS AND METHODS

Study design: Institution based Prospective observational study.
Study setting: The study was conducted in the Department of Medicine, Mathura Das Mathur (MDM) Hospital and Dr. S N Medical College, Jodhpur, India.

Study period: November 2019 to November 2020.
Study subjects: The study was performed in selected patients admitted indoor under the Department of Medicine at M.D.M. Hospital, Dr. S.N. Medical College, Jodhpur. Case selection was based on the diagnostic criteria for AMI that included clinical feature(s) suggestive of myocardial infarction followed by twelve lead electrocardiogram (ECG), serum troponin-I levels and other supportive investigations.

Sample size- 250 patients of STEMI.

INCLUSION CRITERIA:

Consenting adult (≥18 years) male and female patients with typical symptoms of AMI and ECG changes suggestive of STEMI [American heart association (AHA) guidelines].

EXCLUSION CRITERIA:

Patients with past history of Coronary artery disease (CAD), patients who have had previous re-vascularization [Coronary artery bypass grafting (CABG), Per cutaneous trans-catheter coronary angiography (PTCA)], patients presenting with cardiogenic shock, acute left ventricular failure (LVF) or arrhythmia's, patients with sepsis,

pneumonia or other infections, patients with renal insufficiency (creatinine >1.3), pancreatitis, synovitis, patients with persistently derangement liver enzymes (> 5 times upper normal limit)and pregnant women.

DATA COLLECTION:

Patients were recruited in the study after making necessary inclusions and exclusions. The necessary demographic and baseline clinical data were recorded. All the patients underwent blood workup at admission including total leukocyte count (TLC), serum creatinine, liver function tests (LFT), Troponin I by qualitative card test apart from a 12 lead ECG. Serum PCT levels were measured at the time of admission. A chemiluminescent immune-assay system was used for determination of serum PCT level at admission with the normal reference limit being accepted as <0.10 ng/ml and levels above this reference limit were considered elevated. Echocardiography was performed by PHILIPS, En Visor Version C.0.2. Doppler echocardiography on all patients within 5 days of admission.

STATISTICAL ANALYSIS-

All data was analyzed on Statistical Package for the Social Sciences (SPSS) 21.0 statistical package® (SPSS Inc., Chicago, IL, USA). Quantitative variables were expressed with measures of central tendency like mean, median, and measures of dispersion, i.e., standard deviation. Qualitative data was expressed as numbers and percentages. Student's *t* test was used for analyzing parametric variables. Categorical data was analyzed via Pearson's chi-square test. A two-tailed *p*-value of < 0.05 was considered statistically significant. Bivariate correlation was used to calculate association between two pertinent variables.

OBSERVATION AND RESULTS-

A total of 293 patients with STEMI were admitted to our unit during the aforementioned study period. After making the necessary exclusions 250 patients were finally included in the study for analysis (Fig. 1) .

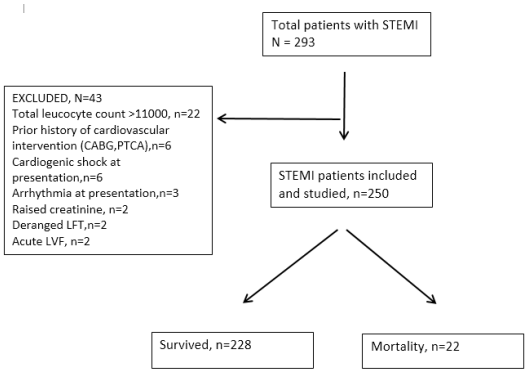

Figure 1.

(CABG-Coronary artery bypass grafting , PTCA- Per cutaneous trans-catheter coronary angiography, LVF- left ventricular failure)

Majority of patients were male (57.60 %) and the mean age of population was 59.77±13.63 years. As compared to males, the mean age of females was significantly higher (55.15±11.42 years vs 66.04±13.94 years respectively, p value <0.0001).The demographic and clinical characteristics of the patients stratified according to gender are shown in Table 1.

Table 1 -Comparison of the demographic and clinical characteristics of patients

Parameters	Gender		Total (Mean±SD)	P value
	Male (Mean±SD)	Female (Mean±SD)		
Number	144 (57.60%)	106 (42.40%)	-	
Age (years)	55.15±11.42	66.04±13.94	59.77+13.63	<0.0001
TLC (cells/µl)	9098.680±1588.9	8835.68±1589.5	8987.17+1591.3	0.131
Creatinine (mg/dl)	1.00±0.22	0.98±0.23	0.99+0.22	0.607
SGOT (IU/l)	95.93±43.55	93.42±41.03	94.87+42.43	0.757
SGPT (IU/l)	58.70±34.63	55.02±31.32	57.14+33.26	0.491
Bilirubin(mg/dl)	0.81±0.28	0.77±0.27	0.79+0.28	0.337
PCT (ng/ml)	1.80±5.30	2.16±4.09	1.95+4.82	0.152
LVEF %	30.74±9.99	30.56±10.89	30.26+10.75	0.747
DM	48.64%	51.35%	14.80%	
HTN	46.34%	53.65%	16.40%	
Thrombolysed	66.01%	33.98%	41.20%	

(TLC – total leukocyte count, SGOT-Serum glutamic oxaloacetic transaminase, SGPT- serum glutamic pyruvic transaminase, PCT-procalcitonin, LVEF- left ventricular ejection fraction, DM- Diabetes mellitus, HTN- hypertension)

CLINICAL ENDPOINTS-

A. PRIMARY ENDPOINT

1. CARDIOVASCULAR COMPLICATIONS- A total of 74/250 (29.6%) patients developed cardiovascular complications in form of cardiogenic shock, heart failure and arrhythmia's. The most commonly encountered complication was cardiogenic shock (n=37, 14.8%), followed by arrhythmia (n=24, 9.6%) and heart failure with reduced ejection fraction (n=13, 5.2%). The various arrhythmia encountered were - left bundle branch block (n=16, 6.4%), q right bundle branch block (n=5, 2%) followed by atrial fibrillation, atrial flutter and ventricular bigeminy in 1 patient each.

Serum PCT levels were elevated in 36/37 (97.30%) patients with cardiogenic shock, 22/24 (91.67%) patients developing arrhythmia's and 12/13 (92.31%) patients developing heart failure. The difference is statistically significant in both the groups ($p < 0.05$) as shown in table 2 and figure 2.

Table 2: PCT level according to the cardiovascular complications

Complications	PCT				Total		P value
	<0.10		≥0.10				
	N=4	%	N=70	%	N=74	%	
A.Carcinogenic shock	1	2.70	36	97.30	37	14.8	<0.0001
B.Heart Failure	1	7.69	12	92.31	13	5.2	0.002
C.arrhythmia	2	8.33	22	91.67	24	9.6	<0.0001
1.LBBB	0	0.00	16	100.00	16	6.4	<0.0001
2.qRBBB	1	20.00	4	80.00	5	2	0.179
3.AF	0	0.00	1	100.00	1	0.4	0.317
4.Atrial flutter	1	100.00	0	0.00	1	0.4	0.317
5.Ventricular Bigemini	0	0.00	1	100.00	1	0.4	0.317

LBBB – left bundle branch block, qRBBB – q right bundle branch block, AF – atrial fibrillation

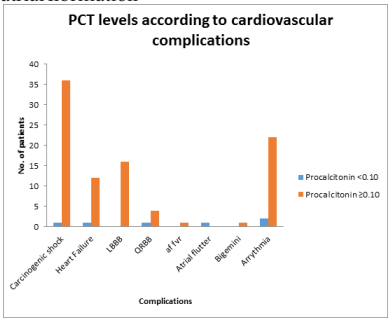

Figure 2-PCT levels according to cardiovascular complications

2. Cardiovascular death

A total of 22/250 (8.8%) patients expired and among them, 21 (95.45%) patients had raised PCT levels. Therefore the risk of death was 10.51 times more in those with raised PCT than those with normal PCT (relative risk =10.51). This association was statistically significant. (p =0.0002) as depicted in table 3, figure 3.

Table 3: Clinical outcome with PCT level

Outcome	PCT				Total	
	<0.10		≥0.10			
	N	%	N	%	N	%
Survivors	109	99.09	119	85.00	228	91.20
Non-survivors	1	0.91	21	15.00	22	8.80
Total	110	100.00	140	100.00	250	100.00

P value 0.0002, 95% CI; 1.542-71.542, **Relative risk 10.51**

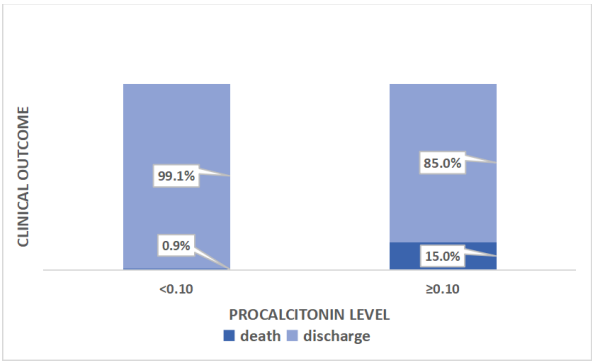

figure-3 : Clinical outcome with PCT level

COMPARISON BETWEEN SURVIVORS AND NON-SURVIVORS

Mean level of PCT was significantly higher in the patients who expired as compared to patients who survived (expired-7.93±10.14 ng/ml, survived- 1.37±3.49 ng/ml, p < 0.0001). Mean left ventricular ejection fraction (LVEF) was significantly lower in the patients who succumbed as compared to the patients who survived (expired-22.72±7.02%, survived- 30.99±10.77%, p=0.0002).The comparison of various parameters between survivors and non-survivors has been presented in table 4.

Table 4: Comparison of parameters in survivors vs non-survivors

Parameters	Outcome		p value
	Discharged (Mean±SD)	Death (Mean±SD)	
Age (years)	59.50+13.60	62.59+13.96	0.254
TLC (cells/µl)	8986.5±1558.1	8994.13±1944.7	0.661
Creatinine (mg/dl)	0.98±0.23	1.08±0.19	0.083
SGOT (IU/l)	94.75±42.11	96.04±46.70	0.998
SGPT (IU/l)	57.99±22.86	48.36±25.15	0.277
Bilirubin(mg/dl)	0.79±0.28	0.76±0.26	0.335
PCT (ng/ml)	1.37±3.49	7.93±10.14	**<0.0001**
LVEF (%)	30.99±10.77	22.72±7.02	**0.0002**

(SGOT-Serum glutamic oxaloacetic transaminase, SGPT- serum glutamic pyruvic transaminase, PCT- procalcitonin, LVEF- left ventricular ejection fraction)

ECHOCARDIOGRAPHIC ASSESSMENT

The mean LVEF in our study is significantly lower in patients with elevated PCT. (LVEF in PCT <0.10- 32.56±10.67 %, LVEF in PCT >0.10- 28.45±10.50%, p=0.003). Thus elevation of PCT correlates with significant LV dysfunction and acts as a negative prognostic marker.

DISCUSSION

Higher PCT levels were significantly associated with increased risk of cardiovascular complications in our study as PCT levels were raised in majority of patients developing cardiogenic shock, arrhythmia's and heart failure and correlated with significant LV dysfunction and acted as negative prognostic marker as mean LVEF was significantly lower in patients with elevated PCT.

The pathophysiological mechanisms linking PCT with adverse outcomes in AMI are likely to be multi-factorial. PCT production could be induced by various stimuli including polytrauma, tissue injury or surgery, due to the release of several cytokines involved in the acute inflammatory response such as IL-1β, IL-2, IL-6 and TNF-α. These cytokines also play a pivotal role in the process of atherosclerosis (27). Erren et al reported that increased PCT concentrations correlated with the extent of atherosclerosis in patients with CAD and peripheral arterial disease. (20) In patients with pre-existing atherosclerosis, ischemia, myocardial injury and inflammatory process that ensues from AMI leads to the production of PCT.(18) We hypothesize that elevated PCT concentrations in the setting of AMI results from non-specific cytokine liberation in the context of local tissue damage to the myocardium caused by ischemia and necrosis. This is consistent with the findings of the study done by Kelly et al (18) wherein they showed that elevated PCT levels were associated with left ventricular dysfunction and an almost 50% higher relative risk of major adverse cardiovascular events at 12 months post-AMI and a negative correlation existed between PCT values and LVEF (r= -0.20 and p= .003) The study done by Patel et al (6) also showed that high PCT level (>1.5 ng/ml) was significantly associated with development of cardiogenic shock and lower LVEF (r= -0.214, p= 0.036).(13) Remskar et al observed a similar association between elevated PCT levels (>0.5 ng/ml) and poor outcomes (severe heart failure and cardiogenic shock) in patients with AMI. (21)

In line with the previously done studies, our findings also suggest that elevation of PCT is significantly associated with higher in-hospital mortality, as 21/22 (95.45%) patients that expired had raised PCT levels. Hence, it can be stated that elevated PCT level is a predictor of cardiovascular mortality in STEMI patients. This association probably results from severe damage to the myocardium after myocardial infarction which leads to release of PCT in blood (22) and hence, when comparing non-survivors with survivors after cardiac arrest, non-survivors have an increased PCT levels between 12 and 24 hours after the onset of AMI (23). This could indicate that non-surviving patients had more severe shock with more severe tissue damage, hypoxaemia and re-perfusion injury which lead to higher PCT levels and in turn was associated with higher complication rates and mortality. The findings from the present study showing association between high levels of PCT with increased mortality in STEMI patients may support this hypothesis, but additional studies need to be carried out in order to confirm this. HE Ataoglu et al (19) observed that among ACS patients, the level of PCT within 48 h after hospital admission predicted mortality. Dominic Kelly et al (18) observed in their study that on Kaplan–Meier assessment, subjects with PCT above the median value (37.0pg ml−1) had a significantly worse prognosis (log rank 27.43, p<0.001). Study by Tejas patel et al (6) also showed PCT level at 24 hours >0.3675 ng/ml showed 80% sensitivity and 81.3% specificity in predicting in-hospital mortality.

Further, the role of PCT in AMI may extend beyond its role as a mere biomarker. Some studies have shown that it may also act as a mediator in facilitating the propagation of myocardial injury. It may do so by modulation of the inducible nitric oxide synthase (iNOS) pathway which can lead to downstream effects on ischemic reperfusion injury.(24,25) Therefore, PCT may also be a potential novel therapeutic target in the management of AMI to improve outcomes. Indeed if our observation of an association with LV dysfunction are corroborated in further studies, PCT inhibition may prevent LV dysfunction and remodeling in the post-MI period and this inhibition may translate to improved patient prognosis.(18) PCT neutralization has already been shown to be feasible and of benefit in sepsis as a method of manipulating the acute inflammatory response (26). However, no studies to date have investigated PCT neutralization in the context of ACS.

Our data have several important clinical implications. First, we demonstrate PCT as a potential biomarker in prognostication of AMI patients. Identification of subjects at risk of adverse outcome at the earliest is of utmost importance. This identification may steer patient management potentially leading to earlier admissions in intensive care units, better monitoring and more aggressive therapy for those patient at high risk and thus leading to better outcomes.

STUDY LIMITATIONS

Our study has certain limitations. Since it is a single-centre study we cannot extrapolate our data to other populations and further multi-centre studies are required to validate our findings. We performed only baseline measurements of PCT (at the time of admission) and therefore cannot clarify the variability of the inflammatory markers during the course of the study. Serial measurements of biomarkers would be of great interest for showing effectiveness of therapeutic strategies and evaluating whether initially determined cardiac risk can be modified by therapeutic interventions. Potentially, the dynamics of PCT levels, rather than absolute values, might be more important for identifying CAD patients with a poor prognosis. We did not follow up of patient beyond the first hospital stay and hence association of PCT with long term prognosis is not known. Our study population included only STEMI patients and we can't comment on association of PCT with NSTEMI or Unstable angina (UA). We do not present data regarding success of re-perfusion therapy which may influence prognosis. In addition, our unit did not provide primary percutaneous coronary intervention at the time of these studies and validation of similar results should be sought in such a population.

CONCLUSION

In conclusion, the findings from the present study suggest that raised PCT level at admission may reflect an inflammatory state and can identify a high risk population as increased PCT levels are associated with higher cardiovascular complications in terms of cardiogenic shock, heart failure, arrhythmia, LV dysfunction and mortality in patients with STEMI.

We demonstrate PCT as a potential biomarker in prognostication of STEMI patients and identifying high risk patients at admission and stratifying them for better management, potentially leading to more aggressive therapy for those at high risk and may represent a potential therapeutic target to improve outcomes. The present results should stimulate experimental and epidemiological studies to further define the precise role of PCT as a marker of cardiovascular disease and prognostic outcome.

DECLARATIONS

There was no financial or other competing interests. The study was approved by the Ethics Committee of the institute. Informed consent was obtained from the subjects involved in the study.

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