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Procalcitonin as a diagnostic marker in Acute Coronary Syndrome

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Abstract

Cardiac biomarkers play a fundamental role in aiding physician for diagnosis of an ACS. They are keys to risk assessment, diagnosis, prognosis, and disease management in cardiovascular disease. Over the course of time, there has been progressive improvement in the tissue specificity of biomarkers. At present, many emerging biomarkers are being studied in relation to ACS. One such marker is the pro-inflammatory marker - procalcitonin. Atherosclerosis is one of the most important causes of ACS. Inflammation plays a major role in the initiation of an atherosclerotic plaque formation. Correct and timely management of an ACS is necessary to prevent complications and mortality. Hence, inflammatory biomarkers may aid in the prediction or diagnosis of an ACS. PCT has drawn much attention and has gradually become a preferred indicator of inflammatory response induced by AMI. Hence, the present study was taken up with the aim to determine the level of serum PCT in ACS, and to compare and correlate its diagnostic value with that of established cardiac biomarkers, cTnI and CK-MB. This is a cross sectional study done in the Department of Biochemistry in collaboration with the Department of Cardiology. 80 cases of Acute Coronary Syndrome were taken and Procalcitonin, serum cTnI & CK- MB was measured. The serum PCT level was found to be raised in all of the 80 cases in this study (>100pg/ml). The present findings in this study provide evidence favoring the clinical value of measuring serum level of PCT as a diagnostic index of ACS.

Keywords: Acute coronary syndrome, procalcitonin (PCT), cardiac troponin I, CK-MB, atherosclerosis.

Introduction

Acute coronary syndrome (ACS) which is one of the sudden killers of many people worldwide, is a broad term that is used to describe a range of condition associated with a sudden reduced blood flow to the heart.

Following an AMI, the different constituents of the myocardium are subjected to cellular injury and death. This initiates an acute pro-inflammatory response and the release of pro-inflammatory mediators which induce the recruitment of inflammatory cells into the MI zone.

Cardiac biomarkers play a fundamental role in aiding physician for diagnosis of an ACS. They are keys to risk assessment, diagnosis, prognosis, and disease management in cardiovascular disease. Creatine kinase MB (CK-MB) is an isoenzyme of the intracellular enzyme creatine kinase and is found almost exclusively in the myocardium. Introduction of CK-MB assay provided a major advance in the early diagnosis or ruling out of MI.2 Following myocardial injury, serum total CK activity and CK-MB isoenzyme rises in parallel. It starts to increase 4-6 hours after injury, peaks at 12-24 hours and returns to baseline after 48-72 hours.3 The diagnostic specificity of serum CK MB for the detection of AMI has been reported to be very close to 100%.4 However, any process that disrupts cardiac sarcolemma membranes (e.g., myocarditis, cardiac trauma, or cardiac surgery including endomyocardial biopsy) can release cytosolic CK–MB. Elevated serum levels of CK–MB are therefore specific for myocardial cellular injury, but not for AMI. Cardiac troponin I (cTnI) is a key component of the Ca2+ regulatory mechanism of cardiac contractility. It is released into the circulation upon ischemia and has become established as one of the principal diagnostic biomarkers of myocardial damage.5 Troponin measurements have some drawbacks. Troponin levels usually do not increase until at least 6 hours after the onset of symptoms. Therefore, a negative result obtained within this period should prompt a repetition of the assay 8 to 12 hours after the onset of symptoms. According to the new criteria issued by the joint committee of the European Society of Cardiology and the American College of Cardiology, elevations of cardiac troponins are fundamental for the diagnosis of myocardial infarction.6 However, there is a risk of misinterpretation of elevated troponin results. Almost 13% of patients presenting with raised high sensitivity cardiac troponin and chest pain eventually prove not to have ACS.7 Over the course of time, there has been progressive improvement in the tissue specificity of biomarkers. However, the quest for a better cardiac biomarker is still an ongoing process. At present, many emerging biomarkers are being studied in relation to ACS. One such marker is the pro-inflammatory marker - procalcitonin.

Procalcitonin (PCT) is a 14.5 kDa peptide composed of 116 amino acids. It is produced by the C cells of the thyroid gland as a precursor of the hormone calcitonin and hence considered as a pro-hormone. In physiological conditions, PCT is produced by the thyroid C cells only but in case of infections and inflammation, PCT is produced by many other extra thyroid tissues like liver, kidneys, lungs and pancreas.8 In healthy individuals PCT levels are below 0.1 ng/ml and thus below the detection limit of PCT in blood.9 The production of PCT during inflammation has been linked with a bacterial endotoxin and inflammatory cytokines (TNF, IL-6). PCT reacts only after 3-6 hours, peaks at 6-8 hours and its level culminates 12-48 hours after endotoxin administration.10 Atherosclerosis is one of the most important causes of ACS. Inflammation plays a major role in the initiation of an atherosclerotic plaque formation.11 Correct and timely management of an ACS is necessary to prevent complications and mortality. Hence, inflammatory biomarkers may aid in the prediction or diagnosis of an ACS.

In recent years, PCT has drawn much attention and has gradually become a preferred indicator of inflammatory

response induced by AMI. There are studies that suggest serum PCT may be used as a marker for AMI.12, 13 So far, data on serum PCT levels in ACS are scarce and controversial14, 15 and to the best of my knowledge, there has not been any study on this topic in this part of the country. Hence, the present study was taken up with the aim to determine the level of serum PCT in ACS, and to compare and correlate its diagnostic value with that of established cardiac biomarkers, cTnI and CK-MB. II.

Materials & methods

This is a cross-sectional study done in the Department of Biochemistry, RIMS, Imphal in collaboration with the Department of Medicine, RIMS Imphal, Manipur from July 2017 to August 2019. The study population consists of 80 patients suffering from Acute coronary syndrome admitted in Medicine Ward or in the Intensive Coronary Care Unit (ICCU) of RIMS, Imphal.

Individuals above 18years who were diagnosed patients of ACS were taken as cases. Patients suffering from fever, burns, medullary thyroid carcinoma, small cell lung carcinoma, end stage renal failure, chronic rheumatoid arthritis and acute mesenteric ischemia, pregnant women and refusal to participate in the study were excluded from the study.

Diagnosis of ACS was made if two or more of the following criteria were fulfilled:

1. Chest pain lasting longer than 30 minutes.
2. Evidence of myocardial ischemia by typical electrocardiogram changes including ST-T changes with or without pathological Q waves in two contiguous leads
3. Elevated levels of biochemical markers of myocardial necrosis (cardiac troponins and CK-MB)

Serum procalcitonin was measured by Human Procalcitonin (PCT) ELISA and serum cTnI was measured by Troponin I(Human cardiac-specific) enzyme immunoassay test kit. Serum CK-MB was measured by CK-MB kit Cliniquant-FSR, IFCC Method. Prior to the commencement of the study, approval from the Research Ethics Board, RIMS, Imphal (Ref No. A/206/REB-Comm (SP)/RIMS/2015/269/12/2017) was obtained. III.

Results and observation

A. Patient demographics

Table 1: Age-wise distribution of cases

Age in years	Cases n (%)
<30	1 (1.3)
31-40	2 (2.5)
41-50	8 (10)
51-60	21 (26.3)
61-70	30 (37.5)
71-80	15 (18.8)
>80	3 (3.8)
Total	80 (100)
Mean ± SD	62.6 ± 10.69

Table 1 shows the number and percentage of cases according to their age group. The study subjects were divided into seven groups according to their age. Maximum (37.5%) of the cases belong to the age group between 61 to 70 years. Mean ± SD of the age of cases was 62.6 ± 10.69 years.

Table 2: Frequency distribution of cases by gender

Gender	n (%)
Male	46 (57.5%)
Female	34 (42.5%)
Total	80 (100%)

Table 2 shows the number and percentage of cases according to gender. 57.5 % of the cases were males and 42.5 % were females.

Table 3: Distribution of presenting symptoms

Presenting symptoms	n (%)
Chest pain	69 (86.3)
Breathlessness	51 (63.8)
Palpitation	21 (26.3)
Sweating	19 (23.8)
Abdominal pain	17 (21.3)
Vomiting	11 (13.8)
Giddiness	8 (10)

Maximum number of the patients presented to the hospital with chest pain (86.3%), followed by

breathlessness (63.8%) whereas, the percentage of cases presented with abdominal pain was 21.3 %.

Table 4: Distribution of cases by diagnosis

Diagnosis	n
STEMI	56
NSTEMI	18
UA	6
Total	80

In table 4, cases were presented according to their diagnosis. Maximum number of cases were diagnosed with STEMI (56), followed by NSTEMI (18). Only 6 of the cases were diagnosed with unstable angina (UA).

Table 5: Median of serum PCT, CK-MB and cTnIin the cases

Parameters	Median	Range
Procalcitonin (pg/ml)	405.00	215.00 – 1200.00
CK-MB (U/L)	58.00	11.00 – 261.00
cTnI (ng/ml)	2.00	0.00 – 59.00

he median values of serum PCT (405.00 pg/ml), CK-MB (58 U/L) and cTnI (2.00 ng/ml) in the cases are shown in table 11. The serum PCT level was found to be raised in all the cases in this study (>100pg/ml).

Table 6: Association of serum PCT with diagnosis

Diagnosis	Serum PCT Mean ± SD (pg/dl)	df	F	p-value*
STEMI	495.46 ± 218.07	2	1.687	0.192
NSTEMI	541.72 ± 283.42			
UA	344.16 ± 76.96			

The mean values of serum PCT was compared among the three forms of ACS i.e., STEMI, NSTEMI and UA. ANOVA test was applied. The mean level of serum PCT was higher in NSTEMI, followed by STEMI and lowest in UA. However, the difference was not found to be statistically significant. (p = 0.192)

Table 7: Correlation between serum PCT and CK-MB & cTnI

Parameters	R	p-value
CK-MB	0.324**	0.003
cTnI	0.573**	0.000

Table 7 shows the correlation of serum PCT with CK-MB and cTnI. Pearson correlation coefficient 'r' was applied. A weak positive correlation between serum PCT and CK-MB was found and it was statistically significant (r = 0.324, p=0.003). Serum PCT was also found to be positively correlated with cTnI and it was also statistically significant (r=0.573, p=0.000)

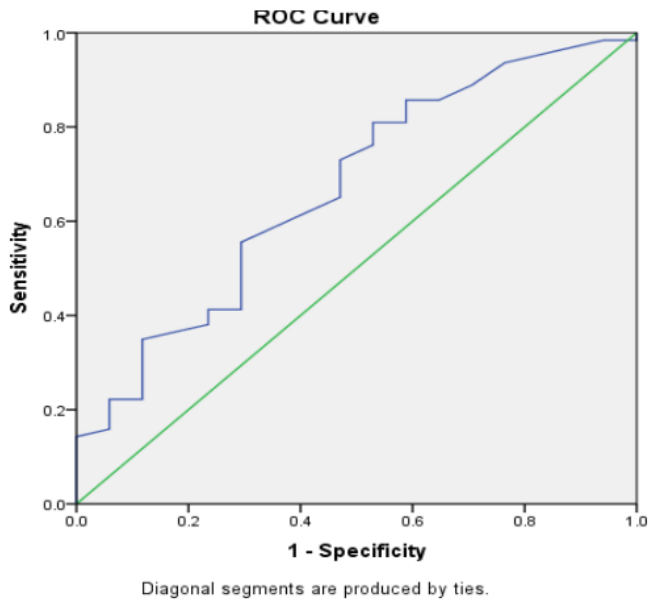

Fig 1: ROC curve showing relation of serum PCT with ACS

Table 8: Area Under the Curve

Test Result Variable(s):	Area	Std. Error[a]	p-value	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Procalcitonin	.670	.074	.032	.525	.815

Area under ROC curve for serum PCT is 0.670, indicating the accuracy of serum PCT to detect ACS is 67%. This was found to be statistically significant (p=0.032)

A cut-off value of 382.50 pg/ml of serum PCT was able to predict the possibility of someone having ACS with 73% sensitivity and 53% specificity.

Discussion

Circulating biomarkers are keys to risk assessment, diagnosis, prognosis, and disease management in cardiovascular disease. They provide clinicians with an important tool for assessment of suspected ACS.17 New candidate markers must add accessible, reliable, and independent new information which contributes to improved clinical management. Although, cardiac troponin I are currently used as "gold standard" biomarkers for diagnosing AMI, the advent of highly sensitive assays for cardiac troponins I and T are accompanied by loss of specificity for AMI.18

A few studies have been conducted to evaluate PCT levels in patients with ACS, but the results were conflicting. As the search for an ideal cardiac biomarker is still ongoing, we conducted this study in an attempt to find out if PCT could be used as a cardiac biomarker.

In the present study, an attempt has been made to evaluate serum PCT levels in ACS patients and correlate its diagnostic performance compared to that of established cardiac biomarkers cTnI and CK-MB. The study population consisted of 80 patients diagnosed with ACS with mean age of 62.6 ± 10.69 years. Maximum (36.5%) of the cases were in the 61-70 years age group. This finding is similar to that of the Multicenter HP ACS Registry19 in which the mean age of the ACS population was found to be 60.9 ± 12.1 years. A study in North Eastern India by Iqbal F et al20 showed the mean age of presentation of ACS was 56.5 years. With advancing age, the risk factor for cardiovascular diseases also increases and hence, more risk for developing ACS.

Males constituted 57.5 % of our study population. Males tend to have MI earlier in life as compared to females. However, the risk of heart disease in women is often underestimated due to the misperception that females are 'protected' against cardiovascular disease.21 Men also have more risk when compared with women. This is because the classical risk factors for CAD like smoking, hypertension, diabetes and dyslipidemia were more common in men.

The majority of our study population came to the hospital with complaint of chest pain (86.3%) and breathlessness (63.8%). Atypical symptoms like burning epigastrium (21.3%) and giddiness (10%) were also recorded. All patients presenting to the Emergency Department (ED) with chest discomfort or other symptoms suggestive of ACS should be considered high-priority triage cases. Evaluation and treatment should follow a predetermined, institution specific protocol for chest pain.22

The study subjects were also divided according to their diagnosis by the cardiologist. These include STEMI, NSTEMI and UA. 70% were diagnosed as STEMI, 22.5% as NSTEMI and the rest 7.5% as UA. STEMI is the predominant form of ACS in India. The CREATE registry also showed that 60% of ACS are constituted by STEMI.23

In the present study, we found that the level of serum PCT was elevated in all cases of ACS [mean ± SD = 494.52 ± 230.20 (pg/ml)]. PCT is a protein that can act as a hormone and a cytokine. PCT levels are low in homeostatic conditions (In our study, serum PCT in ACS is slightly elevated as compared to the very high levels of PCT in conditions like sepsis. This may be because the inflammation that occurs in ACS is only a minor systemic inflammatory response. The increased PCT concentration could be the result of non-specific liberation of cytokines in the context of local tissue damage to myocardium due to ischemia and necrosis.29 The mean level of serum PCT in this study was found to

be higher in NSTEMI, followed by STEMI and lowest in UA. However, the difference was not found to be statistically significant. (p = 0.192) Similar observation was made by Dai et al30 who reported admission plasma PCT level to be higher in myocardial infarction patients than in unstable angina patients. In patients of STEMI, high serum PCT level was found to be associated with in-hospital and 30 days mortality.31 This could be due to the fact that increased PCT concentrations also correlated with the extent of atherosclerosis as reported by Erren et al32 in patients with CAD and peripheral arterial disease. A weak positive correlation was found between serum PCT and CK-MB (r=0.324, p=0.003) and a moderate positive correlation was found with cTnI (r=0.573, p=0.000).

Both were found to be statistically significant. cTnI is currently considered as the gold standard biomarker for AMI. Many patients of ACS developed complications which further increases the duration of hospitalization leading to increase in morbidity and mortality rate due to ACS. Early recognition of complication is of prime importance because appropriate intervention in a timely manner can save lives. 33 Sun S34 suggested that serum PCT can be used as an important diagnostic marker for myocardial infarction complicated by pulmonary infection. In patients admitted in the intensive care unit, the daily increase in the PCT concentrations increases the risk for mortality.35 A number of studies have also reported that PCT provided information on the likelihood of an infectious cause in patients presenting with acute cardiovascular symptoms and therefore provide guidance for management.36 It may also have a prognostic value that correlates with clinical outcome and can potentially guide drug therapy. PCT measurement can be very useful in minimizing the unnecessary use of antibiotics. Hence, very high PCT level in cases of suspected ACS patients can prompt the physician to suspect for some other complication as well. It has been observed in our study that the area under ROC curve for serum PCT was 0.670, which indicated that the accuracy of serum PCT to detect ACS is 67%. This was found to be statistically significant (p=0.032). Various PCT cut-off levels were used in different clinical scenarios to determine the source of an infective process as well as when antibiotic therapy could be utilized or discontinued.39 After the clinician established the cut-off level, it then becomes important to determine the frequency of PCT measurements to determine adequate control. In the present study, at a cut-off value of 382.50 pg/ml, serum PCT was recorded with 73% sensitivity and 53% specificity to predict the possibility of someone having ACS. At present, cTnI are still the most cardiac-specific biomarker even if they are not disease specific. However, a multi biomarker approach is always ideal as it can potentially enhance the diagnostic accuracy and may have broad clinical applications. From this study, it is observed that serum PCT level is increased in ACS. The cause of increase serum PCT concentration is due to ischemia and inflammatory processes. PCT in conjunction with cardiac biomarkers like troponin I and CK-MB has a higher sensitivity in detecting ACS and could be utilized as an early marker for diagnosing ACS.

Conclusion

Given the urgent need for early diagnosis of ACS for appropriate emergency management, a multi-biomarker approach which can enhance the diagnostic accuracy of ACS is always ideal. The present findings in this study provide evidence favoring the clinical value of measuring serum level of PCT as a diagnostic index of ACS. However, further investigation in larger series with serial measurements is recommended to determine the kinetics

of PCT in ACS. Nevertheless, the present results justify further study to evaluate the release of PCT in ACS.

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