Original Research Article

Multi-factorial risk stratification in Acute Coronary Syndrome

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Abstract

Background: ST elevated myocardial infarction (STEMI), non-ST elevated myocardial infarction (NSTEMI) and unstable anginas (UA) are continual spectrum of coronary artery disease (CAD). These are terminal events arising as a result of coronary artery atherosclerosis and superimposed thrombosis.

Materials and methods: A prospective study in which a total of 91 patients of either sex aged 20 to 60 years were recruited, of which 30 were STEMI, 31 were NSTEMI/ unstable angina and 30 were age and sex matched healthy controls. Patients with following complaints of maximum 24 hours duration were registered in the emergency department and were included in the study (ACC/AHA Guidelines, 2002).

Results: In the present study, 91 subjects were recruited from medical emergency department. All of the subjects were meeting the inclusion criteria. Of the total 91 subjects 30 were of STEMI (Group 1), 15 were of NSTEMI (Group 2), 16 were of unstable angina (Group 3) and 30 were controls (Group 4).

Conclusion: In patients of ACS, MPO is raised as compared to controls. Also in complicated ACS, irrespective of other risk factors, MPO was significantly raised as compared to controls and can be used to predict immediate clinical complication. There is no significant association between MPO, hs

CRP and CK-MB when taken together to predict complications. TIMI risk score is a simple prognostication scheme that categorizes a patient's risk of death and ischemic events and provides a basis for therapy.

Key words

Acute Coronary Syndrome, Risk stratification, Myeloperoxidase (MPO), C-Reactive Protein (CRP), Myocardial Infarction, TIMI score, Killips Classification.

Introduction

ST elevated myocardial infarction (STEMI), non-ST elevated myocardial infarction (NSTEMI) and unstable anginas (UA) are continual spectrum of coronary artery disease (CAD). These are terminal events arising as a result of coronary artery atherosclerosis and superimposed thrombosis. Coronary artery disease (CAD) is a modern epidemic, closely following infectious disease in the Indian subcontinent. Indians are likely to account for at least 33.5% of total coronary heart disease (CHD) related deaths by 2015 AD and 60% of all CHD related deaths in the world by 2020 AD. The most common cause of acute coronary syndrome is erosion of an atherosclerotic plaque, resulting in platelet aggregation and thrombus formation. However, any sudden imbalance between myocardial oxygen supply and demand can result in acute ischemia. In unstable angina and non-STEMI, the thrombus is rich in platelets and is usually non-occlusive. In STEMI the thrombus is composed of platelets, fibrin, RBC and occlusion is total or near total There are many traditional biomarkers which initiate, propagate and terminate the process of acute coronary syndrome (ACS), they include proinflammatory cytokines, Interleukin-6, Tumor Necrosis Factor-alpha (TNF-alpha), Matrix Metallo-proteinases (MMP-9), Myeloperoxidase (MPO), Inter Cellular Adhesion Molecule (ICAM), Vascular Cell Adhesion Molecule (VCAM), sCD40L, PIGF, PAPP-A, Acute phase reactant such as C-Reactive Protein (CRP), Brain Natriuretic Peptide (BNP) and pro Brain Natriuretic Peptide (BNP). The Killip classification is a system used in individuals with an acute myocardial infarction , in order to risk stratify them. Individuals with a low Killip class are less likely to die within the first 30 days after their myocardial infarction than individuals with a high Killip class. The TIMI score for acute myocardial infarction with ST-segment elevation was originally described based on eight variables. This score has been described as simple, easily applicable at the bedside and with good discriminatory power for clinical complications and early mortality. This study is done to study the risk stratification of the ACS using MPO, CRP, Thrombolysis in Myocardial Infarction(TIMI) scoring and Killips classification.

Aim and objectives

- To estimate the level of Myeloperoxidase (MPO) in Acute coronary syndrome (ACS) patients (STEMI and NSTEMI/unstable angina)
- To correlate the level of Myeloperoxidase (MPO) with complications in acute coronary syndrome (STEMI and NSTEMI/ unstable angina).
- Risk stratification of the developing complications by using TIMI score and Killips classification.

Material and methods

A prospective study in which a total of 91 patients of either sex aged 20 to 60 years were recruited, of which 30 were STEMI, 31 were NSTEMI/ unstable angina and 30 were age and sex matched healthy controls. Patients with following complaints of maximum 24 hours duration were registered in the emergency department and were included in the study (ACC/AHA Guidelines, 2002). Chief Complaints considered were

- Chest pain or severe epigastric pain, non-traumatic in origin with components typical of myocardial ischemia or MI;
- Central or substernal compression or crushing chest pain, pressure, tightness, heaviness, cramping, burning achy sensation;
- Unexplained indigestion, belching, epigastric pain;
- Radiating pain in neck, jaw, shoulders, back, one or both arms;
- Associated dyspnoea;
- Associated nausea / vomiting;
- Associated diaphoresis.

Exclusion criteria

Treatable cause of angina like thyrotoxicosis or anemia, Abnormal Liver Function Test, Abnormal Kidney Function Test, Bone marrow transplantation, Acute inflammatory reaction, Congenital Heart Disease, aortic stenosis or other valvular lesions, Malignancy, Septicemia and other infections, Pheochromocytoma, Polycythemia, Malignant hypertension, Fever, Congenital myopathy, Connective tissue disorder and Vasculitis.

Results

In the present study, 91 subjects were recruited from medical emergency department. All of the subjects were meeting the inclusion criteria. Of the total 91 subjects 30 were of STEMI (Group 1), 15 were of NSTEMI (Group 2), 16 were of unstable angina (Group 3) and 30 were controls (Group 4). In group 1 out of 30 cases 26 were males and 4 were females. In Group 2 out of 15 cases 13 were males and 2 were females, in Group 3 out of 16, 13 were males and 3 females, in group 4 of total 30 controls 25 were males and 5 females.

Distribution of cases of MI as per ECG diagnosis was as per **Table - 1**. Of the 30 patients as per TIMI score, 15 patients had intermediate to high risk of developing complication (**Table – 2**). Of the total 31 patients, 15 patients had intermediate to high risk of developing complications (**Table – 3**). Of the 30 patients of STEMI, 17 were of class 1, and 13 were of class 2. Of the 15 patients of STEMI, 13 were of class 1, and 1 was of class 2 and 1 was of class 3. Of the 16 patients of UA, 14 were of class 1, and 2 were of class 2 (**Table – 4**).

Table - 1: Distribution of cases of MI.

ECG diagnosis	No of cases
Anterior wall MI	11
Anterolateral wall MI	2
Anteroseptal wall MI	5
Apical wall MI	1
Inferior wall MI	11

Table - 2: TIMI score for STEMI.

Score	No of patients
2/14	3
3/14	4
4/14	1
5/14	3
6/14	4
7/14	7
8/14	4
9/14	3
10/14	1
Total	**30**

Table - 3: TIMI score for NSTEMI / UA.

Score	No of patients
1/7	4
2/7	12
3/7	8
4/7	2
5/7	5
Total	**31**

Risk index (TIME II sub study)

To predict mortality over 24 hours and later on 30 days, in STEMI a simple formulae, as advised by TIME II sub study group, was also applied as per **Table - 5**.

There were 7 patients in risk group 5, 7 patients in risk group 4, 8 patients in risk group 3, 7 patients in risk group 2 and 1 patient in risk group 1. 2 out of 7 patients in risk group 2 developed complications, 3 out of 8 patients group 3 developed complication, 1 out of 7 patients in group 4 developed complication and 5 out of 7 in group 5 developed complications. There were one death in STEMI group and that patient was in risk group 5 (**Table – 6**). Distribution of complications in STEMI/NSTEMI/UA was as per **Table – 7**. Distribution of complication in the 4 groups was significant as per **Table - 8**.

Table - 4: Distribution of Killips class in STEMI / NSTEMI / UA.

Class	STEMI	NSTEMI	UA
1	17	13	14
2	13	1	2
3	-	1	-
Total	**30**	**15**	**16**

Table – 5: Risk Index.

$$\textbf{Heart rate X } \frac{\textbf{(age/10)2}}{\textbf{Systolic blood pressure}} \textbf{ = Risk index}$$

Risk index	Risk group	Risk of death		
		24 hours	In hospital	30 days
≤ 12.5	1	0.3	0.6	0.8
> 12.5 – 17.5	2	0.4	1.5	1.9
> 17.5 – 22.5	3	1.0	3.1	3.3
> 22.5 – 30	4	2.4	6.5	7.3
> 30	5	6.9	15.8	17.4

Table - 6: Distribution of patients of STEMI in various risk groups as per TIME-II substudy.

Risk group	Number of patients n=30	Distribution of complication
1	1	
2	7	2
3	8	3
4	7	1
5	7	4 (1 death)

Levels of myeloperoxidase in study groups

MPO level in group 1 was 13.51±4.63 EU/ml ($p<0.001$), in group 2 it was 15.6±7.07 EU/ml ($p<0.001$), in group 3 it was 11.40±7.07 EU/ml ($p=0.250$), in group 4 it was 8.80±1.67 EU/ml ($p<0.001$). Thus MPO levels in STEMI, NSTEMI and UA was higher as compared to controls. This was statistically significant in case of STEMI / NSETMI and in controls. This was not statically significant in case of unstable angina. When STEMI, NSTEMI and UA were taken as a one group, MPO value was statistically significant as compared to controls (**Table – 9**).

Correlation of MPO levels with complications in ACS

Of the total 59 patients of CAD (STEMI, NSTEMI, and UA) in which MPO determination was done, 17 had complications. In these patients MPO level was higher as compared to 42 patients in whom complications were absent. In patients in whom complications were present MPO level was 17.86±5.75 EU/ml, which was significantly higher, as compared to patients in whom complications were absent. MPO level in these patients was 11.48±4.47 EU/ml. This correlation was statistically significant ($p<0.001$) as per **Table - 10**.

Correlation between MPO, HS-CRP and CPKMB in prognosis of ACS

In our study, hs-CRP levels, though moderately elevated as compared to controls, showed no association with clinical complications arising within 7 days. Similarly CK-MB levels were not associated with complications. Stepwise multiple regression analysis of complications on MPO, hs-CRP and CK MB showed that MPO is the only significant factor contributes to predict complications (**Table – 11**).

Table - 7: **Distribution of complications in STEMI/NSTEMI/UA.**

Complications	**Group 1 (n=30)**	**Group 2 (n=15)**	**Group 3 (n=16)**	**Group 4 (n=30)**
Death	1	0	1	0
Atrial fibrillation	0	0	1	0
Ventricular Tachycardia	1	0	0	0
Post MI angina	4	1	0	0
Shock	1	0	0	0
Bradycardia & Hypotension	3	2	1	0
Frank STEMI elevation	0	0	1	0
TOTAL	**10**	**3**	**4**	**0**

Table - 8: Significance of distribution of complications.

Group	**N**	**Complications present**	**Complications absent**	**Significance**
Group 1	30	10	20	0.002*
Group 2	15	3	12	
Group 3	16	4	12	
Group 4	30	0	30	

Table - 9: level of myeloperoxidase (MPO).

Groups	**Myeloperoxdiase (EU/ml) (mean±SD)**	**Significance**
Group 1 (n=30/30)	13.51±4.63	<0.001*
Group 2 (n=13/15)	15.60±7.07	<0.001*
Group 3 (n=16/16)	11.40±5.92	0.250
Group 4 (n=27/30)	8.80±1.67	<0.001*

Table - 10: Correlation of MPO levels with complications in ACS.

Complications	No of patients	Mean±SD	p-value (one way ANOVA)	Regression equation
Present	17	17.86±5.75	<0.001*	C = 0.41 x MPO – 0.252
Absent	42	11.48±4.47		

Table - 11: Correlation between MPO, HS-CRP and CPKMB in prognosis of ACS.

Dependent factor	Independent factor	r-value	Significant factor	p-value (t-test)
Complications	MPO, hs-CRP, CKMB	0.508	MPO	<0.001*

Discussion

ST elevated myocardial infarction (STEMI), non-ST elevated myocardial infarction (NSTEMI) and unstable anginas (UA) are continual spectrum of coronary artery disease (CAD). These are terminal events arising as a result of coronary artery atherosclerosis and superimposed thrombosis. Coronary artery disease (CAD) is a modern epidemic, closely following infectious disease in the Indian subcontinent. Indians are likely to account for at least 33.5% of total coronary heart disease (CHD) related deaths by 2015 AD and 60% of all CHD related deaths in the world by 2020 AD. The most common cause of acute coronary syndrome is erosion of an atherosclerotic plaque, resulting in platelet aggregation and thrombus formation. However, any sudden imbalance between myocardial oxygen supply and demand can result in acute ischemia. Various biomarkers, acute phase reactants, proteins and other biochemical agents are involved in acute coronary syndromes and it becomes very useful to access these factors individually and in correlation so as to risk stratify the cases.

The TIMI Study Group was founded by Eugene Braunwald, MD in 1984. The group has conducted numerous practice-changing clinical trials in patients with cardiovascular disease or risk factors for cardiovascular disease. Among the group's most important contributions to medicine is the TIMI Risk Score, which assess the risk of death and ischemic events in patients experiencing unstable angina or a non-ST elevation myocardial infarction (NSTEMI).

TIMI Risk Score

In patients with UA/NSTEMI, the TIMI risk score is a simple prognostication scheme that categorizes a patient's risk of death and ischemic events and provides a basis for therapeutic decision making [1].

TIMI Score Calculation (1 point for each):

- Age ≥ 65
- Aspirin use in the last 7 days (patient experiences chest pain despite ASA use in past 7 days)
- At least 2 angina episodes within the last 24hrs
- ST changes of at least 0.5mm in contiguous leads
- Elevated serum cardiac biomarkers
- Known Coronary Artery Disease (CAD) (coronary stenosis ≥ 50%)
- At least 3 risk factors for CAD, such as:
    - Hypertension -> 140/90 or on anti-hypertensives
    - Current cigarette smoker
    - Low HDL cholesterol (< 40 mg/dL)
    - Diabetes mellitus
    - Family history of premature CAD
        - Male first-degree relative or father younger than 55

- Female first-degree relative or mother younger than 65

as systolic blood pressure lower than 90 mmHg) with evidence of peripheral vasoconstriction

Score Interpretation:
% risk at 14 days of: all-cause mortality, new or recurrent MI, or severe recurrent ischemia requiring urgent revascularization.

- Score of 0-1 = 4.7% risk
- Score of 2 = 8.3% risk
- Score of 3 = 13.2% risk
- Score of 4 = 19.9% risk
- Score of 5 = 26.2% risk
- Score of 6-7 = at least 40.9% risk

The TIMI Risk Score for STEMI is also useful for patients with known STEMI. Though these patients have a clear protocol - normally thrombolysis or Percutaneous coronary intervention - and are already high risk for mortality, the TIMI Risk Score for STEMI provide risk stratification which helps treatment decisions after acute issues have been resolved [2].

The Killip-Kimball classification has played a fundamental role in classic cardiology, having been used as a stratifying criterion for many other studies. Worsening Killip class has been found to be independently associated with increasing mortality in several studies. The Killip classification is a system used in individuals with an acute myocardial infarction , in order to risk stratify them. Individuals with a low Killip class are less likely to die within the first 30 days after their myocardial infarction than individuals with a high Killip class.

- **Killip class I** includes individuals with no clinical signs of heart failure.
- **Killip class II** includes individuals with rales or crackles in the lungs, an S_3, and elevated jugular venous pressure.
- **Killip class III** describes individuals with frank acute pulmonary edema.
- **Killip class IV** describes individuals in cardiogenic
  shock or hypotension (measured

C-reactive protein (CRP) was identified by Tilet and Francis (1990) in the plasma of patients with pneumonia, and was named for its ability to bind and precipitate the C-polysaccharide of pneumonococcus [3, 4]. It is an alpha globulin with a molecular mass of identical subunits, which are noncovalently assembled as a cyclic pentamer [5]. CRP is syntheized in the liver and is normally present as a trace constituent of serum or plasma at levels of less than 0.3 mg/dl [6, 8, 10].

CRP is one of the acute-phase proteins, the serum or plasma levels of which rise during general, non-specific response to a wide variety of diseases. This includes infections by gram-positive and gram-negative organisms, acute phase of rheumatoid arthritis, abdominal abscesses, and inflammation of the bile duct [5]. CRP may also be found in patients with Guillain-Barre syndrome and multiple sclerosis, certain viral infections, tuberculosis, acute infectious hepatitis, many other necrotic inflammatory diseases, burned patients and after surgical trauma [5, 7, 8].

Although the detection of elevated levels of CRP in the serum is not specific for any particular disease, it is a useful indicator of inflammatory processes [9]. CRP levels rise in serum or plasma within 24 to 48 hours following acute tissue damage, reach a peak during the acute stage and decrease with the resolution of inflammation or trauma [3, 10, 11]. Levels of C-reactive protein are elevated in patients with unstable angina, a condition that is probably dependent on coronary thrombosis of atherosclerotic plaques, but not in those with variant angina caused by vasospasm. Therefore, elevated C-reactive protein levels in patients with acute coronary syndromes likely reflect inflammation in the coronary artery rather than in the ischemic myocardium. In acute coronary syndrome CRP predicts recurrent MI independently of troponin, which suggests it is

not merely a marker for the extent of myocardial damage. Recent data also suggest that hsCRP may be a marker for risk of restenosis. Elevated hs-CRP levels also seem to predict prognosis and recurrent events in patients with stroke and peripheral arterial disease. However, CRP levels are not very sensitive in MI and ACS as several factors have been identified as being associated with increased to decreased levels of CRP.

Myeloperoxidase is a hemoprotein (molecular mass of 140 kDa) consists of a pair of heavy and light chains. It is stored in azurophilic granules of polymorphonuclear neutrophils and macrophages and functions to catalyse the conversion of chloride and H_2O_2 to hypochlorite. Myeloperoxidase is released into the extracellular fluid and general circulation during inflammatory conditions. This enzyme has been implicated in the oxidation of lipids contained within LDL.

Several studies support potential links between MPO and the development of CAD. Myeloperoxidase has been implicated as a participant in atherosclerosis through mechanisms related to its role in inflammation [12, 13], LDL oxidation and nitric oxide consumption leading to endothelial dysfunction [14]. Myeloperoxidase generates an array of diffusible oxidants [12] and is capable of initiating lipid peroxidation and promoting protein nitration and corsslinking [15] processes known to occur during the evolution of atherosclerosis [12, 16-20]. Myeloperoxidase also binds to LDL in plasma and promotes site-specific oxidation of the lipoprotein. Both immunohistochemical and mass spectrometry studies demonstrate that MPO is present in, and promotes oxidative modification of targets within human atheroma at all stages of lesion development. Furthermore, LDL recovered from human atherosclerotic lesions is enriched in multiple oxidation products formed specifically by MPO, such as chlorotyrosine and Schiff base adducts of p-hydroxyphenylacetaldehyde (a tyrosine oxidation product) with both apolipoprotein B100 lysine residues and aminophospholipids. There are several clues to the potential functional consequences of MPO catalysed oxidation in the artery wall. Isolated human monocytes use MPO to oxidatively convert LDL into an atherogenic particle capable of promoting cholesterol accumulation and foam cell formation. Uptake occurs via the scavenger receptor CD36, a receptor that appears to play a major role in foam cell formation in vivo. Myeloperoxidase may thus be involved in the atherscleroitc process direct by promoting lesion development. Myeloperoxidase also may play a role in the pathogenesis of acute coronary syndromes through plaque destabilization. Circulating leukocytes release MPO during acute coronary syndromes. Macrophages containing MPO and MPO dependent oxidation products are selectively enriched in atheromas that have undergone plaque rupture and ulceration. Moreover hypochlorous acid (HOCI) a primary oxidant generated by MPO, may promote extracellular matrix degradation in vivo. Myeloperoxidase-generated HOCI both activates latent matrix metalloproteinases and inactivates their physiological inhibitors (e.g. tissue in inhibitor of metalloproteinase 1). Myeloperoxidase thus may influence plaque stability and the propensity for provoking thrombosis.

Myeloperoxidase also may contribute to CAD through promoting endothelial dysfunction. Nitric oxide modulates MPO catalytic activity and serves as a physiological substrate for MPO. Myeloperoxidase attenuates nitric oxide-dependent smooth muscle relaxation and preliminary studies with preconstricted vascular rings show that MPO attenuates nitric oxide mediated vasorelaxant responses [21]. Thus, MPO may serve as a catalytic sink for nitric oxide, limiting its bioavailability and function [22, 23].

Conclusion

To conclude, in patients of ACS, MPO is raised as compared to controls. Also in complicated ACS, irrespective of other risk factors, MPO is

significantly raised as compared to controls and can be used to predict immediate clinical complication. There was no significant association between MPO, hs CRP and CK-MB when taken together to predict complications. TIMI risk score is a simple prognostication scheme that categorizes a patient's risk of death and ischemic events and provides a basis for therapy.

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