HIGH SENSITIVITY C-REACTIVE PROTEIN, LEUKOCYTE AND DIFFERENTIAL COUNT IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF **D.M. (BRANCH-II) CARDIOLOGY** EXAMINATION OF **THE TAMIL NADU DR.MGR MEDICAL UNIVERSITY, CHENNAI**, TO BE HELD IN **FEBUARY-2007**

CERTIFICATE

This is to certify that the thesis titled "HIGH SENSITIVITY C-REACTIVE PROTEIN, LEUKOCYTE AND DIFFERENTIAL COUNT IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION" is the bonafide work of **Dr. Yerra Shivakumar** done towards partial fulfillment towards requirements of the D.M. (Branch-II) (Cardiology) Examination of the Dr. MGR Medical University, Chennai, Tamil Nadu, to be conducted in Febuary 2007.

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ACKNOWLEDGEMENTS

I would like to thank my patients who participated in the study without which the study would not have materialized. I thank God for helping me to finish it successfully. All along, there have been people who helped me and without whom this thesis would not have been possible.

I am immensely grateful to my professors, Dr. Jacob Jose and Dr. George Joseph, who provided all the factual guidance encouragement and support for my thesis at all status. I thank them for having patiently gone through my thesis and suggesting several valuable changes.

My special thanks to Prof. Sunil Thomas Chandy and Dr. Paul George, other faculty members and my colleagues who had guided me through out my study.

I would like to express my thanks Dr. Selvakumar and Dr.Victoria (Clinical Biochemistry department) for all the help rendered in doing the hs-CRP assay. My sincere thanks to the staff of Cardiology department for all the help rendered to me in completing the study.

Dr.Yerra Shivakumar

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High-Sensitivity C-reactive protein, Leukocyte and Differential Count in Patients with Acute Myocardial Infarction

Introduction

Coronary artery disease remains the leading cause of serious morbidity and mortality in adults. Although standard risk factors account for most of the risk profile in the population, they do not explain the picture in its entirety.[1] Half of all myocardial infarctions occur in persons in whom plasma lipid levels are normal.[2] The advancement in the understanding of pathophysiology of atherosclerotic vascular disease have thrown new insights regarding potential indicators of underlying atherosclerosis and cardiovascular risk. Due to absence of usual clinical symptoms, detection of preclinical atherosclerosis in patients is a challenging job. The development of an atherosclerotic plaque involves a complex interaction between the endothelium, inflammatory cytokines and various blood elements (Figure 1, 2). In an effort to identify patients at high risk for cardiovascular events, several novel risk markers have been proposed for use in screening.

Inflammation is thought to play a key role in the pathogenesis of coronary artery disease. C-reactive protein (CRP), a marker for inflammation, is a prognostic marker for stable angina pectoris, unstable angina and non-Q wave myocardial infarction.[3,4]

In addition to CRP an elevated white blood cell (WBC) count has been associated with the development of coronary artery disease and long-term mortality.[5] WBC count is an inexpensive and routine measurement that can be performed on admission to the accident and emergency department ; it would be of great benefit to understand if the WBC count has any relationship with the risk of developing further complications following acute myocardial infarction (AMI).

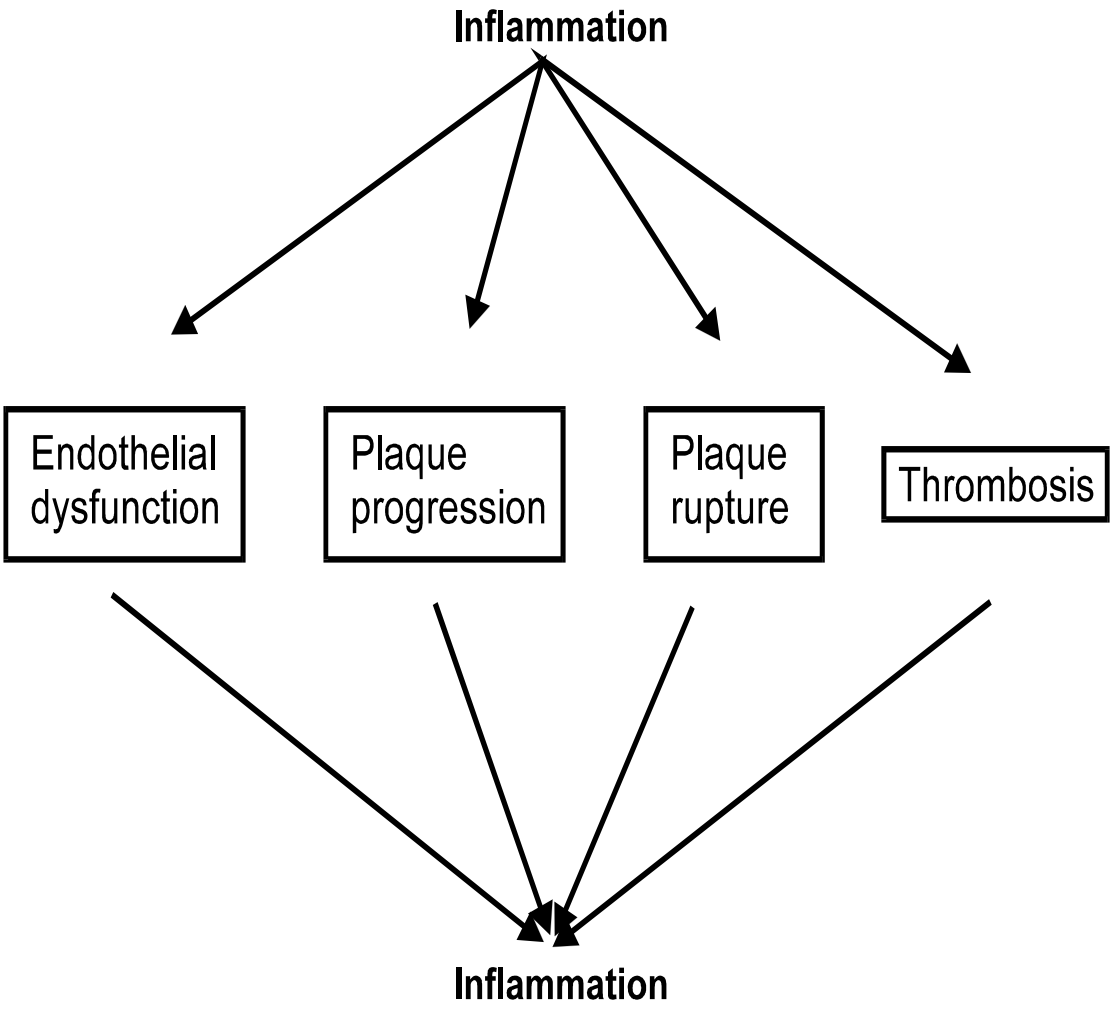


Figure 1. Inflammation leads to endothelial dysfunction, plaque progression, plaque erosion and rupture, and thrombosis. These events themselves lead to further inflammatory marker/mediator release, leading to a dangerous cycle that may cause recurrent ischemic events.

In this prospective study, we aimed to investigate the association between hs CRP and white cell count, obtained on admission, and the development of subsequent in hospital adverse events in patients with an acute ST segment elevation myocardial infarction. Previous studies did not contain information regarding the WBC differential count and it's correlation with the hs CRP level and short-term prognosis, which might have contributed important additional information.

Aim & Objectives

Aim:

To assess the association of high sensitivity C-reactive protein and white cell count to in-hospital complications of STEMI.

Objectives:

1. To evaluate the prognostic value of CRP measured as high sensitivity C-reactive protein assay (hs-CRP) in patients with ST segment elevation myocardial infarction.
2. To investigate the relationship between total and differential WBC count obtained on admission with parameters such as LV systolic function and the development of post MI complications during the hospital course.

Review of Literature

Inflammation plays a crucial role in the biology of atherosclerosis. In recent years, it has been recognized that atherogensis represents an active inflammatory process rather than a simply passive injury with infiltration of lipids. Inflammation characterizes all phases of atherothrombosis and provides a critical pathophysiological link between plaque formation, acute rupture, leading to occlusion and myocardial infarction. Formation of fatty streak, the earliest phase of atherogenesis, involves recruitment of leukocytes due to the expression of adhesion molecules on endothelial cells; in turn triggered by inflammatory cytokines such as interleukin-1 and tumor necrosis factor-alpha. Subsequent migration of inflammatory cells into the subendothelial space requires chemotaxis controlled by chemokines, induced by primary cytokines. Mononuclear cells within initial infiltrate as well as intrinsic vascular cells release growth factors that stimulate proliferation of smooth muscle cells and lead to plaque progression. Thrombotic complications of plaque s often involve physical disruption associated with both local and systemic inflammation. Several mediators or markers of inflammation and various sources have been described (Figure 2). Table 1 shows the assay of inflammatory markers, which have potential for clinical use.

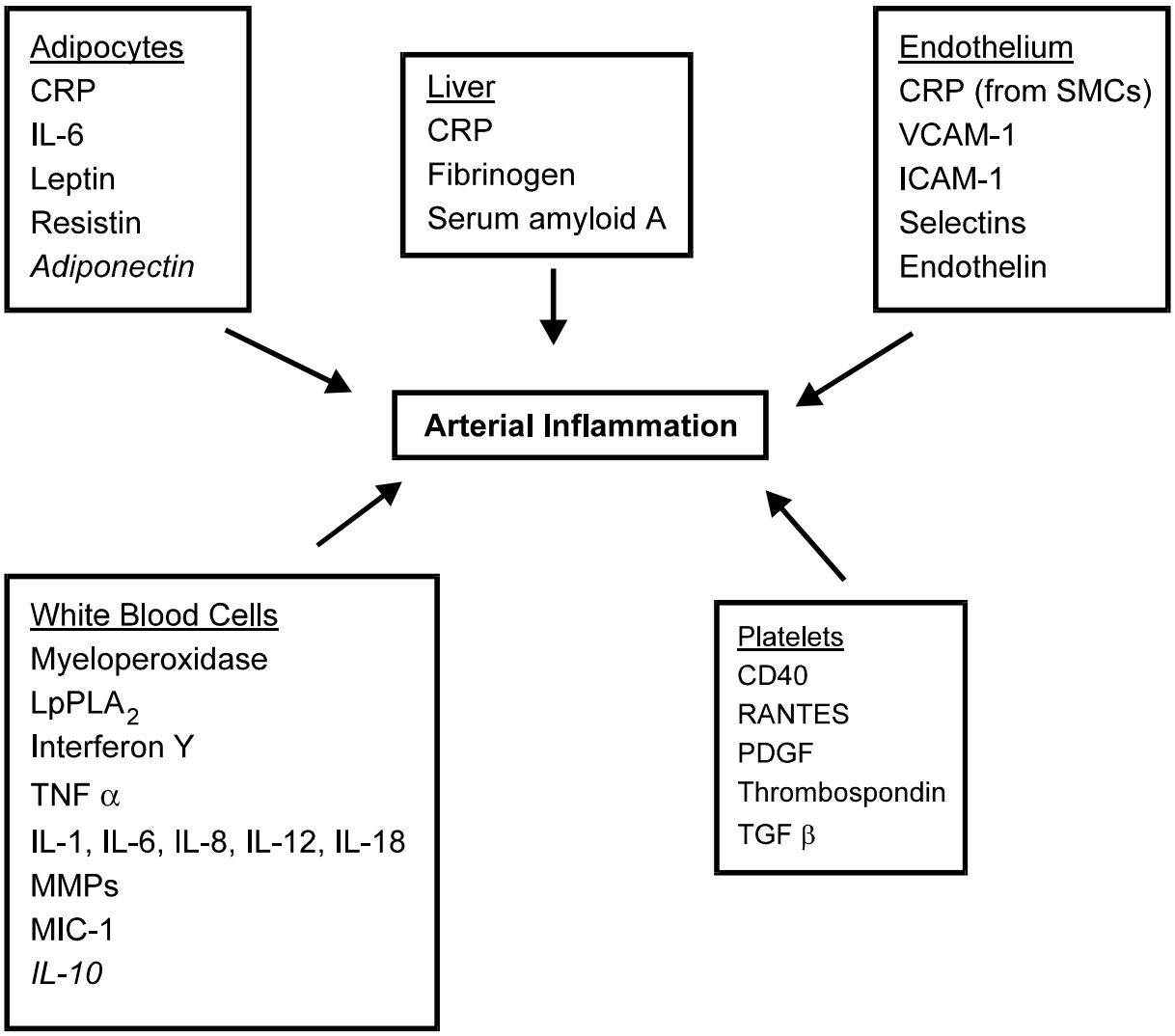


Figure 2. There are several inflammatory mediators from various sources that participate in arterial inflammation. Numerous different cell types participate in the process of arterial inflammation. In the context of arterial inflammation, most of these mediators are viewed as deleterious. However, the ones in italics are believed to be beneficial CRP, C-reactive protein: ICAM, intercellular cell adhesion molecule;IL, interleukin; $LpPLA_2$ lipoprotein-associated phospholipase A2; MIC-1, macrophage inhibitory cytokine-1: MMp1 matrix metalloprolelnase; PDGF, platelet derived growth factor, RANTES, regulated on activation normally T-cell express and secreted; SMCs, smooth muscle cells; TGF, transforming growth factors TNF, turnor necrosls factor; VCAM, vascular cell adhesion molecule.

Table 1. Assays of inflammatory Markers for Potential Clincal Use[6]

Analyte	Stability	Assay Availability	World Health Orgainsation Standards Available
Soluble adhesion molecules (e.g.,E-Selectin, P-Selectin, Intracellular adhesion molecule-1)	Unstable (Unless frozen)	Limited	No
Cytokines (e.g., interleukin-1b, -6, -8, and 10 and tumor necrosis factor -a)	Unstable (Unless frozen)	Few	Yes
Acute-phase reactants			
Fibrinogen	Unstable (Unless frozen)	Many	Yes
SAA	Stable	One	Yes
hs-CRP	Stable	Many	Yes
WBC count	Stable	Many	Yes

High-Sensitivity C - reactive protein:

The primary proinflammatory cytokines result in messenger cytokines such as interleukin -6, which travel from local site of inflammation to the liver, where it triggers a change in the program of protein synthesis, characteristic of acute phase response. The acute phase reactant, C-reactive protein (CRP), a simple down stream marker of inflammation has emerged as a major cardiovascular risk factor and as the “golden marker” for inflammation.[7] CRP is a circulating member of pentraxin family that plays a major role in the human innate immune response. Although it is primarily derived from the liver, recent data

indicate that cells within human coronary arteries, particularly from the atherosclerotic intima can elaborate CRP. Recently improved high sensitive and standardized quantitative assays in serum have allowed a re-evaluation of its potential as a diagnostic laboratory test. hs-CRP level has been proven to be a marker for risk stratification in primary cardiovascular disease prevention. The predictive values of hs-CRP are significantly higher than other traditional biochemical cardiovascular risk markers like total cholesterol, HDL-cholesterol, LDL-cholesterol, lipoprotein (a), homocysteine, apoliprotein A1 and B.

C reactive protein Structure:

Tillet & Fransis first described C-reactive protein in 1930. They concluded that sera of patients suffering from acute infection, precipitated with a non-protein pneumococcus extracts, called C-polysaccharide in the presence of calcium ions. The protein that caused this reaction was called C-reactive protein (CRP).[8] It belongs to pentraxin family of proteins (PTX-1); ability to form pentameric structures formed by non-covalent interactions, and hence the name.(Figure 3a). CRP is a mature chain 206 aminoacid, non-glycosylated, ubiquitous protein found in both vertebrates and invertebrates. Each protomer has the characteristic “lectin fold”, composed of a two-layered sheet with a flattened jellyroll topology (Figure 3b). The ligand-binding site composed of loops with two calcium ions is located on the concave side.

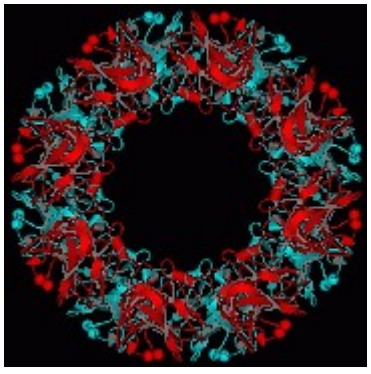


Figure - 3a

Negatively stained electron micrograph showing the typical pentameric disc-like structure of hs-CRP [8]

Figure 3b

Ribbon diagram of the crystal structure, showing the lectin fold and the two calcium atoms (spheres) in the ligand-binding site of each protomer of hs-CRP [8].

CRP is composed of 5 identical (pentraxin), 23KD subunits. It is produced in the liver (Chromosome 1q21-23). It is detectable on the surface of about 4% of normal peripheral blood lymphocytes. It has a half-life of 18 to 20 hours. The median concentration of CRP in healthy young adults is 0.8 mg/L, the 90th centile is 3.0 mg/L and the 99th centile is 10mg/L. CRP value tends to slightly increase with age. It is a stable compound and shows little variation in repeated measurements. There is no significant diurnal variation or difference between fasting and non-fasting values.

Why C reactive protein is a strong predictive biomarker?

Choosing CRP as a predominant biomarker of cardiovascular events, is due to some of its potential advantages over other biomarkers.[9]

CRP has:

- Long half-life (18 to 20 hours)

- Lack of age and sex dependence
- Lack of diurnal variation
- It is also a factor of proatherogenesis
- Long-term stability during storage (no special collection procedure)

CRP is a more sensitive and reliable indicator of inflammatory process than the ESR and the leukocyte count. The serum CRP concentrations increase faster than that of the ESR and when the condition subsides, CRP falls very quickly, reaching normal levels, several days before the ESR normalizes. Rises in CRP are only one part of a number of intricate changes in serum proteins and enzymes, but it can be a parameter that can be measured early.

Functions And Mechanisms Relating C-Reactive Protein (CRP) To The Development And Progression Of Atherothrombosis:

CRP binds to a variety of autologous and extrinsic ligands. Autologous ligands include plasma lipoproteins, damaged cell membranes, phospholipids etc. Extrinsic ligands are mainly constituents of microorganisms such as capsular and somatic components of bacteria, fungi and parasites. After binding, CRP activates the classical complement pathway and the terminal membrane attack complex. Activation of complement causes opsonization and enhances phagocytosis of the various ligands. Thus, CRP is thought to contribute to host defense against infection and may also protect against autoimmunity.

The function of CRP is related to its role in the innate immune system. Similar to IgG, it activates complement, binds to Fc–receptors and acts as an opsonin for various pathogens.[11] Interaction of CRP with Fc–receptors leads to the generation of proinflammatory cytokines that enhance inflammatory response.

Unlike IgG, which specifically recognizes distinct antigenic epitopes, CRP recognizes altered self and foreign molecules based on pattern recognition. Thus, CRP is thought to act as a surveillance molecule for altered self antigens and certain pathogens. This recognition provides an early defense and leads to a proinflammatory signal and activation of the humoral adaptive immune system. Thus, a number of functions have been ascribed to CRP, including initiation of opsonization and phagocytosis and activation of complement, neutrophils and monocyte-macrophages. Collectively these properties imply an important role for CRP in the recognition of microbial organisms and as an immunomodulator in the host defense. CRP may also be important in the recognition of necrotic tissues. It binds to phospholipids of damaged cells with subsequent limited activation of the complement system and enhanced uptake of these cells by macrophages.

CRP binds to apoptotic cells, protects cells from assembly of the terminal complement components and sustains an anti-inflammatory innate immune response. CRP binds with high affinity to chromatin. It has been proposed that one of its major physiologic functions is to act as a scavenger for chromatin released by dead cells during the acute inflammatory process. Thus, CRP has both recognition and an effectors function. Determination of CRP is of a great value in diagnosis, treatment and monitoring of inflammatory conditions. CRP may influence directly vascular vulnerability through several mechanisms (Figure 4,5), including enhanced expression of local adhesion molecules, increased expression of endothelial PAI-1, reduced endothelial nitric oxide bioactivity, altered LDL uptake by macrophages, and co-localization with complement within atherosclerotic lesions.

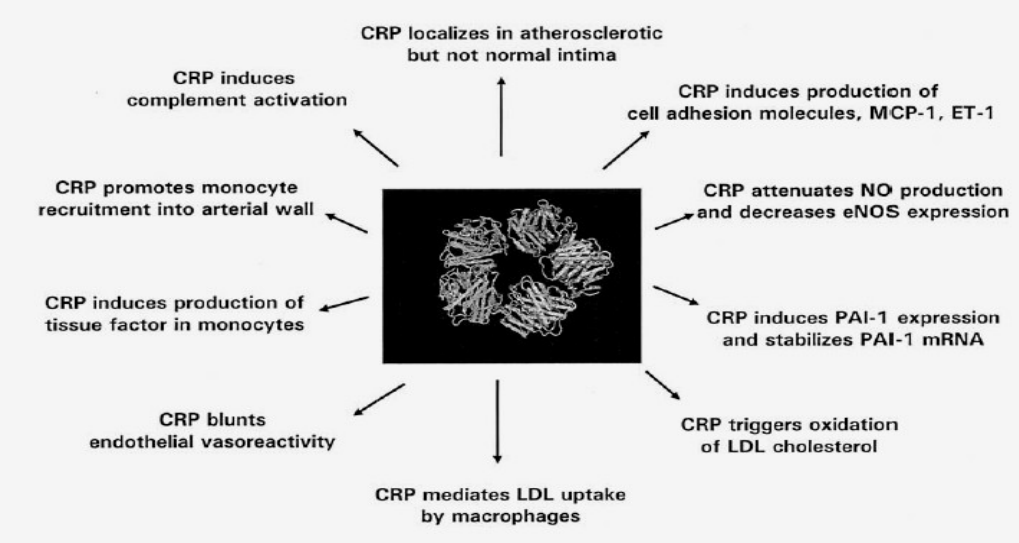


Figure 4. Mechanisms relating C-reactive protein (CRP) to the development and progression of atherothrombosis.[12]

CRP has proatherogenic properties [13,14]

• It leads to the activation of:

Endothelial cell adhesion molecules (ECAMs)
Intercellular adhesion molecule-1 (ICAM-1)
Vascular cell adhesion molecule-1 (VCAM-1)

Selectin-E&P

Monocyte Chemo attractant protein-1 (MCP-1)

- Recruits monocytes into the arterial wall
- Blunts endothelial activity
- Stabilizes plasminogen activator inhibitor-1(PAI-1) mRNA
- Decreases endothelial nitric oxide synthase expression
- Activates nuclear factor-kappa

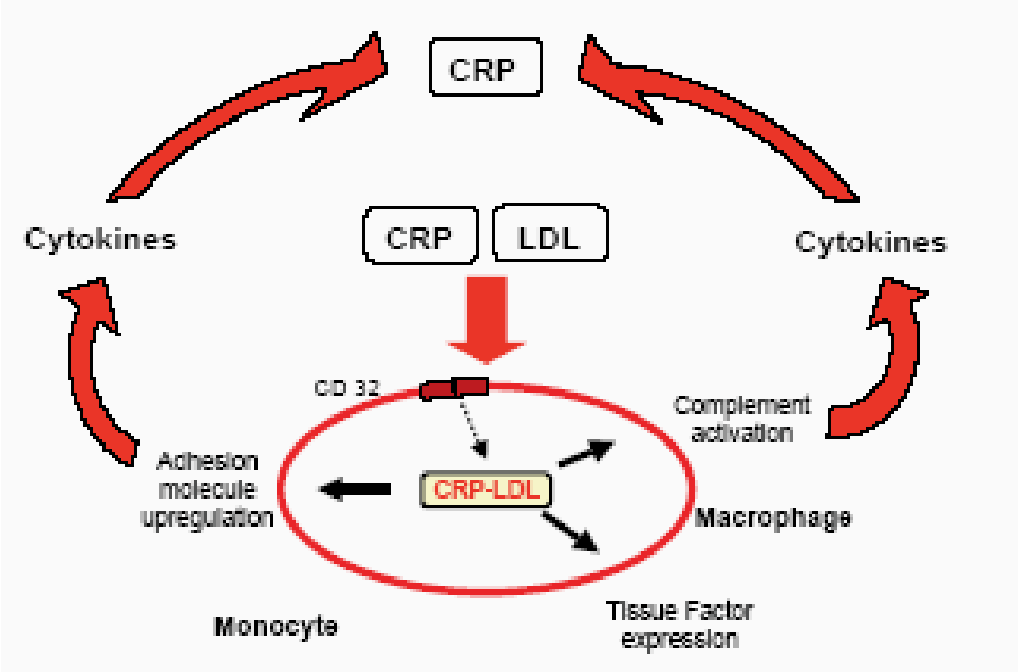


Figure 5. CRP colocalizes with LDL-C and, following its specific receptor-directed uptake into monocytes, 1) stimulates tissue factor expression, 2) complement activation, and 3) adhesion molecule up-regulation.[15]

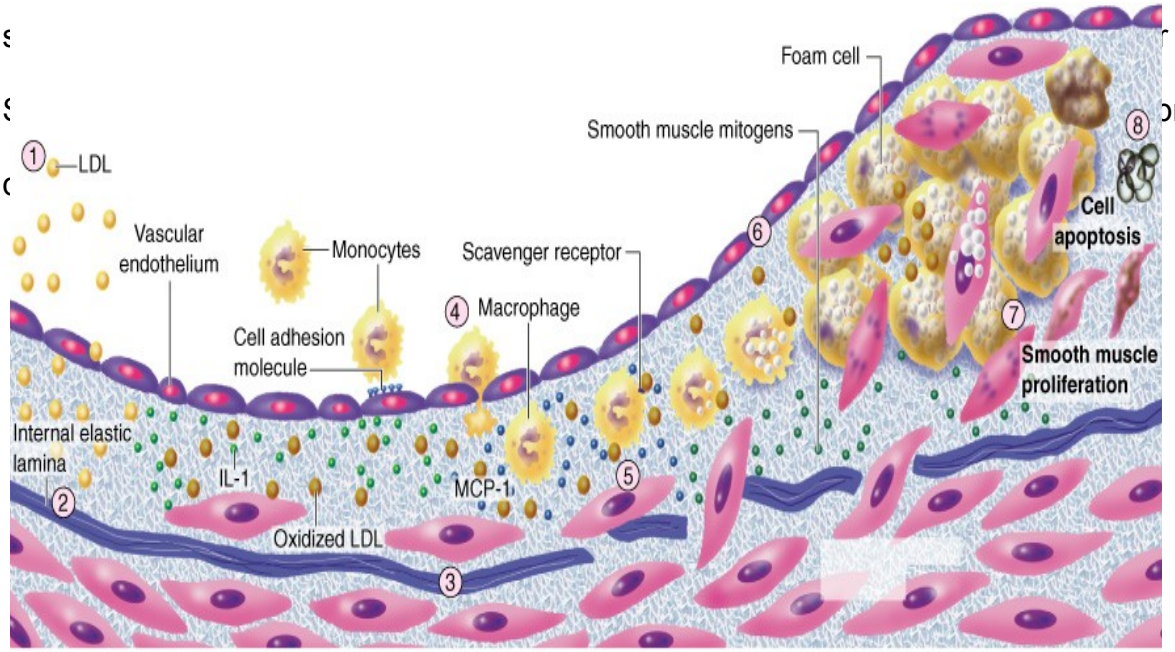
CRP has been shown to be deposited in human atherosclerotic plaques, especially the complex ones, and the locally concentrated CRP may be present in sufficient amount to promote the development of the atherosclerosis.[14] CRP activates macrophages to express cytokines and tissue factor (TF) and enhances the uptake of LDL.[14] CRP also amplifies the proinflammatory effects of several other inflammatory mediators, including endotoxin.[15] A key

feature in the inflammatory hypothesis of atherosclerosis is the recognition of circulating immune cells and recruiting to the inflamed vessel by interacting with adhesion molecules and cytokines.

Role of CRP and Endothelial dysfunction:

Recently, it has been suggested that CRP also affects nitric oxide (NO) pathways[16, 17] relating to the association between endothelial dysfunction and atherosclerosis. CRP is an important regulator of tone of both resistance and conduit vessels in vivo.[18] CRP leads to the induction of IL-6 (Inter leukin-6) and ET1 (Endothelin-1), there by decreasing the expression and bioavailability of e-NOS in endothelium,[16,17,18] but human and rat experiments showed functionally active highly purified human CRP directly increased rather than decreasing nitric oxide bioavailability in blood vessels in vitro, in contrast to earlier reports.[17] So CRP can have specific, direct effects on vascular function via nitric oxide pathways.[18]

Evolution of the atherosclerosotic plaque and role of hs CRP: The cytokines thus induced increase expression of adhesion molecules for leukocytes that cause their attachment and chemoattractant molecules that direct their migration into the intima. Blood monocytes upon entering the artery wall in response to chemoattractant cytokines such as monocyte chemoattractant protein 1 (MCP-1), encounter stimuli such as macrophage colony



receptors.

promote the

Figure 6. Schematic of the evolution of the atherosclerosotic plaque [19]

Macrophage foam cells are a source of mediators such as further cytokines and effector molecules such as hypochlorous acid, superoxide anion (O_2^-), and matrix metalloproteinases. Smooth muscle cells migrate into the intima from the media and smooth muscle cells in the intima divide. Smooth muscle cells divide and elaborate extracellular matrix, promoting extracellular matrix accumulation in the growing atherosclerotic plaque. In this manner, the fatty streak can evolve into a fibrofatty lesion. In later stages, calcification can occur and fibrosis continues, sometimes accompanied by smooth muscle cell death (including programmed cell death) yielding a relatively acelluar fibrous capsule surrounding a lipid-rich core that may also contain dying or dead cells and their detritus (see figure 6). [19]

Despite the importance of CRP in the management of acute coronary syndromes, very few studies have addressed the relation between lesion morphology and CRP. Sano et al suggested that the presence of ruptured plaque is only related to elevated CRP in patients with AMI less than six hours. As mentioned previously CRP is mainly synthesized and

secreted by hepatocytes 6 hours after an acute stimulus and shows rapid turnover (with a half-life of 19 hours). Myocardial necrosis also promotes the synthesis of CRP. [20] Sano et al included patients in his study with AMI treated within 6 hours of the onset of symptoms. There was no elevation in CK-MB and Troponin T at admission, which suggests that elevated CRP levels may reflect properties of the coronary lesions just before rupture but are unlikely to reflect myocardial necrosis. Plaque rupture occurs most frequently at the point where the fibrous cap is thinnest and most heavily infiltrated by macrophage foam cells. These rupture-related macrophages are activated, indicating ongoing inflammation at the site of plaque disruption. Macrophages are capable of degrading the extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasminogen activators and the family of matrix metalloproteinases, that may weaken the fibrous cap, predisposing it to rupture and suggested that elevated CRP may reflect the activity of activated macrophages in the atherosclerotic plaque also plays an important key role in plaque disruption.[20] Ridker et al studied immunohistochemical staining for CRP, in patients who had sudden death associated with severe coronary artery disease and reported that CRP may correlate with the number of thin-capped atheromas that can be considered vulnerable plaques and also suggested that CRP is elevated in the setting of “active” angina and that elevated CRP may be a predictor of a future risk of the onset of AM.[21] Ridker et al results may help to explain why elevated CRP may predict the future onset of AMI. It has also been reported that coronary calcium deposition may be a feature of atherosclerosis and plaque rupture and may predict future coronary events.[9] This has led to speculation that coronary calcium deposition may be related to CRP. However, the evidence for a relation between coronary calcium and CRP on electron beam computerized tomography studies is controversial. Both coronary calcium and CRP independently contribute risk stratification towards the incidence of cardiovascular events. Neither superficial nor deep calcium deposition, as identified by IVUS, is associated with CRP

elevation and suspect that elevated CRP and calcium deposition reflect a different pathological status in patients with AMI.[20] Normal CRP group, 44% were non–rupture type lesions. Pathological evaluation has shown that AMI caused not only by plaque rupture but also by plaque erosion, which is a major substrate for coronary thrombosis in AMI and eroded proteoglycan-rich and smooth muscle cell–rich plaques lack a superficial lipid core, are less likely to see plaque rupture, and have fewer foci containing macrophages. Non-ruptured lesions are thought to cause a less inflammatory response compared with ruptured lesions. [20]

hs-CRP and acute myocardial infarction :

MI is invariably associated with a major CRP response. The peak value of CRP occurs about 50 hours after the onset of pain in MI. In patients who recover uneventfully, the CRP falls rapidly towards normal in the usual exponential fashion, reach baseline over 3-5 days. However, complications such as persistent cardiac dysfunction, further infarction, aneurysm formation, intercurrent infection, thromboembolism are associated with either persistently raised CRP levels or secondary increase after the initial decrease. European Concerted Action on Thrombolysis and Disabilities study showed that elevation of CRP levels by 20% or more was found in survivors of MI and it increases further if other sites, such as peripheral vasculature are also involved.[25] Hence CRP may serve to represent the inflammatory burden. Monitoring Trend and Determinants in Cardiovascular diseases Trial[45] showed that highest CRP level has 2.6 times higher risk of MI. Bazzino et al[23] reported that post infarction angina occurred in only 14% of patients with a normal CRP level, by comparison, 64% of patients admitted with high CRP levels had evidence of post infarction angina, nearly 42% required revascularization, and 21% had recurrent MI. Walter et al [24] reported that in patients with MI, increased CRP concentration is associated with the presence of complex angiographic lesions and the need for revascularization.

It was demonstrated that in the patient group with unstable angina or non-Q wave MI, abnormal CRP levels on admission and elevated levels of troponin I are important for the incidence of major cardiac complication within six months.[24]

Evidence that hs-CRP is a predictor of adverse events in the stable phase after MI is less consistent than evidence of its prognostic ability in primary prevention or in acute coronary settings. In the Cholesterol and Recurrent Events (CARE) secondary prevention trial of pravastatin, patients with elevated hs-CRP levels at 3 to 20 months after the index MI were at higher risk of recurrent events during the 5-year follow-up period.

Data from Physician Health Study (PHS),) showed that CRP is a stronger predictor of cardiovascular events than LDL. Paul Ridker et al[27] showed that when risk estimates with 95% confidence intervals are compared for the each marker,hs-CRP and hs-CRP + total cholesterol: HDL-C ratio had the highest prediction of relative risk of future cardiovascular events. Because it disappears rapidly when inflammation subsides, CRP detection signifies the presence of a current inflammatory process. Further, by serial measurements important information can be obtained on the resolution or continuation of the inflammatory process. CRP has been shown in multiple randomized controlled trials that, it can predict incidence of MI, stroke, peripheral arterial disease, sudden cardiac death, recurrent ischemia and death in chronic stable angina, acute coronary syndromes and cardiovascular events in those undergoing PCI.

CRP value as a predictor of risk has recently been questioned. Danesh et al reported that CRP concentration was a relatively moderate predictor of the risk of CAD and added only marginally to the predictive value of established risk factors for CAD. They reported that, after adjustment for baseline values for established risk factors, the odds ratio for the CAD was 1.45 (95%CI 1.25 to 1.68) in a comparison of participants in the group with respect to baseline CRP.[28]–

hs-CRP and first coronary events :

Ten prospective studies, 6 in USA and 4 in Europe, have consistently shown that hs-CRP is a powerful predictor of future first coronary event in apparently healthy men and

women. Multiple Risk Factors Intervention Trial (MRFIT) demonstrated a direct positive association between hs-CRP and CAD mortality in men followed over a 17-year period (RR = 2.8; 95% CI, 1.4 – 5.4). This relationship, however, was evident only among smokers. A similar association between hs-CRP and future coronary events was noted in the Cardiovascular Health Study and Rural Health Promotion Project, which included men and women over 65 years of age with subclinical cardiovascular disease. The Physician's Health Study (PHS), demonstrated similar positive association between hs-CRP and future coronary events in apparently healthy men. Unlike the observation in MRFIT, however, this association was evident in both smokers and nonsmokers. This study showed that those in the highest quartile of hs-CRP had a 2-fold higher risk of future stroke (RR = 1.9; 95%CI, 1.1 – 3.3), 3-fold higher risk of future MI (RR= 2.9; 95% CI, 1.8 – 4.6), and 4-fold higher risk of future peripheral vascular disease (PVD); (RR = 4.1; 95% CI, 1.2 – 6.0). The relative risks were stable over a long period of time (6 years) and independent of other CAD risk factors. The European MONICA (Monitoring Trends and Determinants in Cardiovascular disease) Augsburg study showed that an increase of one standard deviation in the log-transformed value of hs-CRP was associated with a 50% increase in coronary risk and that subjects with hs-CRP concentrations in the highest quintile had a 2.6-fold higher risk of developing future coronary events. Helsinki Heart Study confirmed these observations and demonstrated that those in the highest quartile of hs-CRP had a more than 3-fold higher risk of future MI or cardiac death (RR = 3.56; 95%CI, 1.93 – 6.57). The Women's Health Study (WHS) showed that hs-CRP is a strong predictor of future events in women (RR = 4.4; 95% CI, 2.2 – 8.9). In stratified analysis, hs-CRP continued to be a strong predictor of future cardiovascular events even among subgroups of women with no history of hyperlipidemia, hypertension, smoking, diabetes or family history of CAD. [21] The hs-CRP concentrations seen in these postmenopausal women were some what higher than those reported previously in men.

Although no difference in hs-CRP values was noted between premenopausal women and age-matched males, recent reports showed that hormone replacement therapy (estrogen alone or estrogen and progestin) is associated with increased hs-CRP concentrations.[31] These findings suggest that the increased hs-CRP seen in the WHS subjects may reflect the influence of hormone replacement therapy rather than the effect of gender.

hs CRP after percutaneous coronary intervention :

Elevated CRP levels may also represent a biomarker for patients who are susceptible to re-occlusion. In patients with stable CAD, who underwent stent implantation following angioplasty, CRP levels increased over 96 hours in those with restenosis. In patients without restenosis, CRP levels peaked at 48 hours and then declined. In patients who have stable angina and disease in one vessel and have stent placement, normal CRP levels before the procedure or normalization of CRP levels within 72 hours after coronary artery stent placement identifies a large subset of patients who are unlikely to have cardiovascular events during the twelve-month follow-up.[29]

Zebrack et al [30] followed 2554 patients undergoing coronary angiography for evaluation of symptoms of stable (65%) or unstable (35%) angina. In this cohort, 72% of patients received medical therapy only, 9% received angioplasty, and 19% received bypass surgery. After 2 years of follow-up, hs-CRP levels of 10 mg/L or higher (vs <10 mg/L) were predictive of death or future MI in patients with CAD (Relative risk [RR], 2.1; 95% CI, 1.5-3.1) and patients without CAD (RR, 2.3; 95% CI, 0.9-5.5). Moreover, CRP retained predictive value at each quintile of CAD severity. Indeed, the absolute risk of death or MI among patients with the lowest CAD scores(i.e., those with normal angiograms) and the highest hs-CRP levels (11.1%) exceeded the risk for patients with the highest CAD scores and the lowest hs-CRP levels (8.4%), despite a higher prevalence of traditional coronary risk factors in the group with more extensive CAD. A similar pattern of results was observed for the outcome of MI alone.[30]

The precise source of CRP elevations remains unclear. In a small study, hs-CRP levels did not change after PTCA in patients with stable or unstable angina and normal pre procedural CRP levels but did increase after PTCA in patients with unstable angina and elevated hs-CRP levels at baseline. These data suggest that plaque rupture per se may not be the source of elevated hs-CRP levels among persons with unstable angina; instead, elevated hs-CRP in this setting may be a marker of hyper responsiveness of the inflammatory system to even small stimuli underlying inflammation i.e, those with elevated levels of hs-CRP. Few data are available regarding hs-CRP in the setting of coated stents. However, because sirolimus and similar coatings present an antiproliferative, anti-inflammatory surface interface with the endothelium, these stents likely will decrease event rates the most among individuals with the highest levels of CRP. It has been demonstrated that there was an increase in procoagulant activity in patients who underwent successful primary angioplasty for AMI and that this increase in procoagulant activity was associated with an increase in Mac-1 expression on circulating leukocytes. Finally, the adherence of activated platelets to polymorphonuclear leukocytes via Mac-1 may also play a role in thrombus formation. Patients with an elevated WBC count had reduced patency and greater thrombus burden and had a poorer downstream microvascular perfusion as assessed with TIMI perfusion grade. This impaired myocardial perfusion reflects leukocyte-mediated endothelial dysfunction and microvascular plugging, as described in animal models.

Leukocyte in cardiovascular disease

The leukocyte count is a marker of inflammation that is widely available in clinical practice. Correlation of the leukocyte count with CAD and investigations into the utility of the leukocyte count as a risk factor and prognostic indicator in patients with CAD are consistent with the current concept that atherosclerosis is an active inflammatory process rather than simply passive injury with infiltration of lipids. According to this concept, monocytes are recruited from the peripheral blood into the vessel wall after endothelial injury. The recruited monocytes differentiate into macrophages that phagocytose lipids and secrete metalloproteinase enzymes.

Table 2. Mechanisms by which leukocytosis may predispose to ischemic vascular events

Prothrombotic effects

1) Synergism with platelets in providing a catalytic surface for thrombin generation, including receptors for fibrinogen and proteolytic activity that can activate coagulation factor intermediates and platelets,
2) Platelet–leukocyte aggregates and transcellular metabolism
3) Prothrombotic alteration of fibrinogen by post-translational, myeloperoxidase-enhanced nitrating oxidants

Vascular effects

1) Rheologic compromise of microvasculature by adhesion, aggregation, platelet recruitment, and obstruction
2) Release of proinflammatory and vasculotoxic factors, reactive oxygen species, proteases, eicosanoids, growth factors, interleukins, and myeloperoxidase

Acceleration of atherosclerosis

1) Monocyte infiltration
2) Leukocyte-dependent oxidation of low-density lipoprotein and HDL
3) Platelet–leukocyte aggregates
4) Contribution to intimal hyperplasia after vascular injury

Proteolytic and oxidative vascular damage: Leukocytes may influence the development of CAD through their ability to cause proteolytic and oxidative damage to coronary arteries. Stimulated neutrophils are known to: 1) secrete proteolytic neutral proteases that promote the detachment of endothelial cells from vessel walls and the adherence of platelets to subendothelial collagen and fibronectin; 2) release large amounts of the chemotactic agent leukotriene B_4 in patients with stable angina; 3) secrete large amounts of inflammatory mediators and 4) release superoxide anions in hyperlipidemic patients. Some researchers have observed increased neutrophil aggregation and oxidase activity in the coronary sinuses of patients with angiographically documented CAD.[39] Oxygen-free radicals play an important role in the atherosclerotic process, but their destructive effects can be prevented, at least in theory, by antioxidant enzymes such as superoxide dismutase and catalase proteolytic enzymes are another likely source of arterial damage.

Vessel plugging: Leukocytes may influence the development of CAD through their ability to affect blood flow through the cardiac microvasculature and because they are stiffer and larger than either red blood cells or platelets, leukocytes may obstruct small nutrient vessels. In patients with acute MI, the leukocytosis that follows necrotic injury usually although not always renders leukocytes less deformable and less able to pass through the microvasculature, thus aggravating ischemia, extending the infarct area, and leading to further complications. Adhesion molecules on leukocytes become up regulated or down regulated in atherosclerosis, hence increasing chemotaxis of monocytes beneath the endothelium in early stages of atherosclerosis.

Abnormal leukocyte aggregation: Abnormal leukocyte aggregation may play a role in CAD similar to platelets and granulocytes aggregate when stimulated. In patients with peripheral vascular disease, increased platelet number and activity, neutrophil count, and acute-phase reactant protein levels correlate with increased plasma, serum, and blood viscosity and mononuclear leukocytes become less filterable during periods of ischemic pain. Abnormal leukocyte aggregation and high leukocyte count may even be seen as a manifestation of hematologic stress syndrome.[40]

Leukocytes and infarct expansion : During reperfusion of ischemic myocardium, neutrophils and platelets can plug capillaries in the coronary microcirculation, resulting in the no-reflow phenomenon, ventricular arrhythmia, loss of coronary vascular reserve, infarct extension, and even organ dysfunction. The vascular obstruction may be partly due to the [illegible] dothelium integrins such as CD18B and adhesion molecules such as i[illegible]. Support for this idea comes from the observation that treatment with C[illegible]s well as the observation that a deficiency in either CD18 or ICAM-1 ca[illegible]tion and myocardial necrosis after MI-reperfusion injury.[41] The mecha[illegible]uced infarct expansion remains unclear. Perhaps reperfusion further i[illegible], resulting in the accumulation of neutrophils (see figure 7) that then w[illegible]y unleashing more destructive oxygen-derived free radicals, proteases, and leukotrienes. This view is borne out by experimental studies showing the cardioprotective effects of neutrophil inhibition and the interference of monoclonal antibodies in interactions between leukocytes and endothelium.

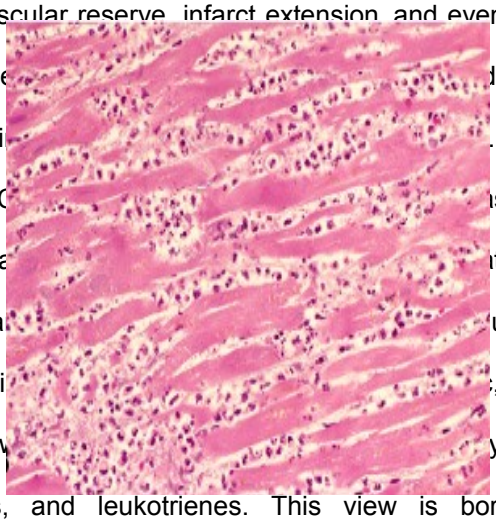


Figure 7. Dense polymorphonuclear leukocytic infiltrate in an area of acute myocardial infarction of 3 to 4 days duration

Leukocytes and hypercoagulability: Leukocyte count correlates positively with coagulation factors, including fibrinogen and factors VII and VIII.[69] It is also known that the systemic inflammatory response that usually follows successful reperfusion involves the expression of cytokines (interleukin (IL)-1-beta, IL-8, and IL-6) and adhesion molecules [macrophage adhesion molecule (MAC)-1] on circulating monocytes, which in turn leads to increased monocyte procoagulant activity.[70] Both IL-6 and -8 exert their procoagulant effects in a time- and dose-dependent fashion and at concentrations found in the peripheral blood of patients with acute MI. MAC-1-a beta$_2$integrin that mediates the adhesion of leukocytes to vessel walls, catalyzes the conversion of factor X to factor Xa and binds fibrinogen mediating the adherence of activated platelets to neutrophils and any thrombosis that may follow.

Leukocytes and reperfusion: The leukocyte count immediately after a coronary event may influence the chances of successful reperfusion. One study of patients undergoing thrombolytic therapy after an acute MI[42] found that those with higher non-neutrophil count at presentation achieved successful reperfusion (i.e., TIMI flow grade 3) more often. This observation may be due to the fact that a longer time from symptom onset to treatment was associated with a higher neutrophil count and a lower non-neutrophil count, and this delay in treatment has affected the response to reperfusion. In general, an increased leukocyte count immediately after acute MI has been associated with poorer myocardial reperfusion, higher mortality, increased risk of new-onset CHF or shock, thromboresistance, and greater thrombus burden.[43] The increased thromboresistance, may be due to the enhanced generation of thrombin at sites of vascular injury by circulating monocytes and neutrophils that have been recruited to such sites. The enhanced thrombin production is mediated by interactions between P-selectin glycoprotein ligand-l expressed by leukocytes and P-selectin expressed by activated platelets and by the monocytes themselves. These interactions make the membrane surface available for the assembly and function of coagulation complexes involved in tissue factor-initiated thrombin production.

Leukocytes and electrical instability : Leukocyte count may affect the electrical stability of the heart. A study by Maisel et al has shown that a high leukocyte count is a significant predictor of ventricular fibrillation in patients who have suffered an acute MI.

White cell count and Lesion Morphology :

In addition to neutrophils mast cells that secrete or induce degradative proteases begin to accumulate in the plaque. Over time, the recruitment and accumulation of inflammatory cells increase the lipid and inflammatory cell content of the plaque and cause extensive neovascularization of involved adventitia and intima. The atherosclerotic plaque becomes more vulnerable to rupture, leading to cardiovascular events. When plaque rupture does occur, it is usually followed immediately by mural or occlusive coronary thrombosis and dynamic vasoconstriction on exposed intimal tissue in or near areas of luminal inflammation.[32,33] Plaque rupture occurs most frequently at the point where the fibrous cap is thinnest and most heavily infiltrated by macrophage foam cells. These rupture-related macrophages are activated, indicating ongoing inflammation at the site of plaque disruption.

Macrophages are capable of degrading the extracellular matrix by phagocytosis or by secreting proteolytic enzymes such as plasminogen activators and the family of matrix metalloproteinases that may weaken the fibrous cap, predisposing it to rupture. Burkers etal in a pathological study reported that eroded proteoglycan-rich and smooth muscle cell–rich plaques lack a superficial lipid core, are less likely to plaque rupture, and have fewer foci containing macrophages.[20] Non ruptured lesions are thought to cause a less inflammatory response compared with ruptured lesions.

WBC and percutaneous coronary intervention Thus, regardless of the mechanism underlying the association between leukocytosis and mortality after acute myocardial infarction, it appears that reperfusion and early revascularization strategies mitigate or eliminate the association between WBC count and mortality during the first 6 months after a myocardial infarction. Bhatt etal.[67] data suggest that patients who are not eligible for, or who do not receive, reperfusion or revascularization therapy may be a more appropriate group in which to test the effect of interventions to lower the WBC count. Many epidemiologic and clinical studies have shown leukocytosis to be an independent predictor of future cardiovascular events, both in healthy individuals free of CAD at baseline and in patients with stable angina, unstable angina, or a history of myocardial infarction. This relationship has been observed in prospective and retrospective cohort studies, as well as in case-control studies. It is strong, consistent, temporal, dose-dependent, and biologically plausible. The relationship persists after adjustment for multiple CAD risk factors, including smoking.

It has been demonstrated that there was an increase in procoagulant activity in patients who underwent successful primary angioplasty for AMI and that this increase in procoagulant activity was associated with an increase in Mac-1 expression on circulating leukocytes. Finally, the adherence of activated platelets to polymorphonuclear leukocytes via Mac-1 may also play a role in thrombus formation. Patients with an elevated WBC count had

reduced patency and greater thrombus burden and also had a poorer downstream microvascular perfusion as assessed with TIMI perfusion grade. One option is that this impaired myocardial perfusion reflects leukocyte-mediated endothelial dysfunction and microvascular plugging, as described in animal models of ischemia reperfusion. When comparative analyses were conducted within a single study, the association between mortality after myocardial infarction and leukocyte count was less dramatic in patients who underwent reperfusion or early revascularization treatment than in those who did not receive these therapies. Thus, in the National Registry of Myocardial Infarction 4 (n=115 273), the mortality odds ratio (comparing the highest to the lowest quartile of leukocyte count) was 4.0 for those not undergoing reperfusion therapy (n=83 775), and the absolute in-hospital mortalities were 18.6% and 4.7%, respectively, for the highest and lowest WBC count quartiles, whereas the comparable odds ratio for those undergoing reperfusion therapy with thrombolytic agents or primary percutaneous coronary intervention (PCI; n=30 954) was 2.7 (9.3% versus 3.5%). These data yield absolute differences in mortality between the highest and lowest WBC count quartiles of 13.9% for those not receiving reperfusion therapy and 5.8% for those receiving such therapy.[37]

Leukocytes and acute myocardial infarction:

The association between leukocytosis and increased morbidity and mortality of ischemic vascular disease has been observed [for] more than half a century. Recent studies >350,000 patients confirm robustness of the association and dramatically higher relative and absolute acute and chronic mortality rates in patients with high versus low WBC count.[43] Whether elevated white cell count is a marker of the inflammatory process or is direct risk factors for acute myocardial infarction remains unclear. [37] An elevated WBC count has been to be independent predictor of long term mortality and all cause mortality there have been few studies[64,65] examining the association WBC count and early death.

A study from National Registry of Myocardial Infarction (NRMI), evaluated the association between WBC count at admission and in-hospital mortality following AMI in 115,273 patients at 1,189 hospitals in the United States. They observed a strong association between WBC count and in-hospital mortality of AMI patients. After adjustment for patient demographics, medical history, presenting clinical characteristics, and treatment factors, patients in the higher WBC count quartile remained with significantly increased odds of death. This association was independent of age, gender, and reperfusion status, with increasing WBC count associated with progressively higher mortality. The unadjusted odds ratio (OR) four versus the first quartile showed strong associations with in-hospital mortality among entire population was 4.09 (95%CI =3.83 to 4.73) and following adjustment for covariates, the magnitude of the odds ratio attenuated, but odds ratio remained significant (OR: 2.71[95%CI= 2.53 to 2.73]). [37]

Epidemiologic studies also have demonstrated correlations between the white blood cell count and the risk of acute myocardial infarction and stroke. Early studies have shown that patients with elevated white blood cell (WBC) count were at higher risk of mortality and recurrent AMI. More recent studies have confirmed the association between an elevated WBC and clinical outcomes in AMI patients and furthermore suggested that WBC could serve as a simple and inexpensive tool for risk stratification in acute coronary syndromes.[34]

An elevated WBC count may be a marker for chronic inflammation secondary to tobacco smoking as well as to other factors, and this inflammation could contribute to ischemic risk, Recent advances in the understanding of microvascular injury, leukocyte activation, and hemorrheology strengthen the hypothesis that WBCs are major contributors to microvascular injury and atherogenesis and that chronic leukocytosis reflects ischemic risk in a direct rather than an indirect manner.

Keskin et al have shown that elevation of WBC count during AMI is associated with

adverse outcomes. They also found an association between high WBC count and 30-day MACE, failed to reach statistical significance (p 0.059). This finding is clinically important and encourages the use of this parameter for the risk of stratification of patients with AMI.[45,61] Understanding of microvascular injury, leukocyte activation, and hemorrheology strengthen the hypothesis that WBCs are major contributors to microvascular injury and atherogenesis and that chronic leukocytosis reflects ischemic risk in a direct rather than an indirect manner. As early as 1954, Cole et al. reported that AMI patients with WBC count higher than 15,000 cells/mm^3 who were admitted to the hospital had a risk of death within 2 months that was four times as great as the risk of patients with normal WBC count (<10,000 cells/mm^3).[46] Maisel et al reported that the WBC count on admission to the hospital was an independent predictor of early ventricular fibrillation. 3% of patients with normal or modestly elevated WBC count (>15,000 cells/mm^3) suffered ventricular fibrillation, while 15% of patients with more elevated WBC count experienced ventricular fibrillation.[44] Furmanand etal examined the relationship between WBC and short-term prognosis following AMI, and found that patients in the uppermost quintiles of WBC were more likely to have a complicated hospital course and more extensive acute myocardial necrosis.

In-hospital mortality in relation with WBC count in115,273 patients in the National Registry of Myocardial Infarction 4. Showed that a J shape relation of the data with patients with high WBC count and very low WBC count constituting a subgroups with higher mortality (Figure 8).[37]

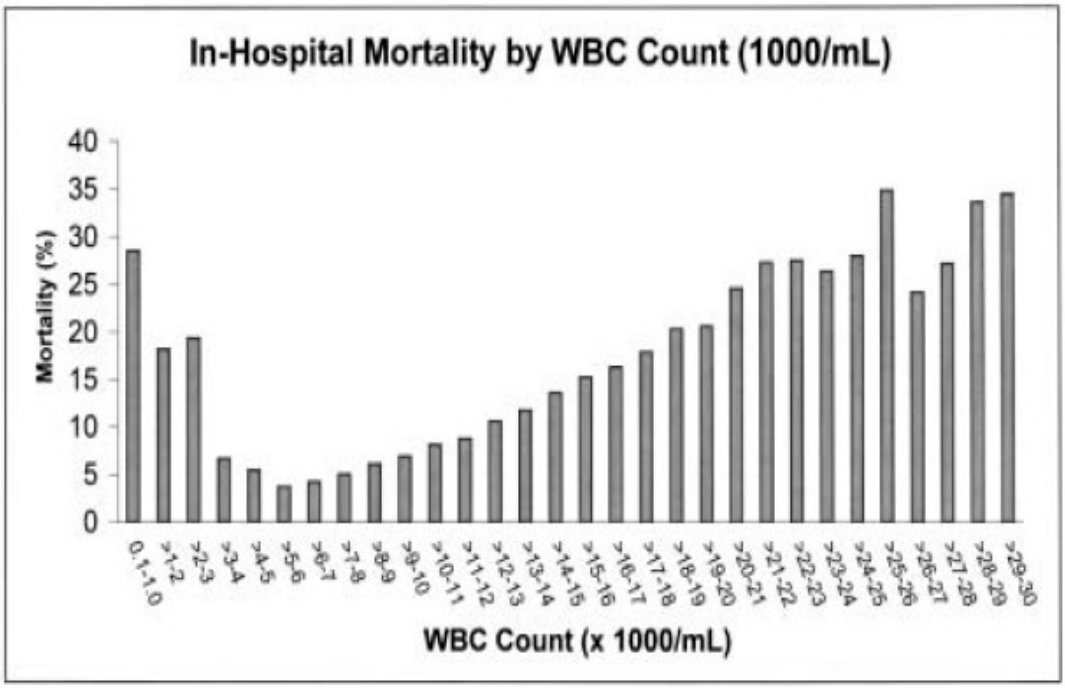


Figure 8. A J-shaped relationship between mortality and leukocyte count was observed in National Registry of Myocardial Infarction 4 study.[37]

As suggested by Gurm et al, a very low WBC count may indicate general poor health and thus confer additional mortality risk independent of the coronary artery disease. In addition, he suggested that inclusion of such a subgroup in the analysis might dilute the association between the WBC count and cardiovascular risk in the remaining population.[36] Barron et al, reported on pooled data on 992 patients from the Thrombolysis in Myocardial Infarction (TIMI) 10A and 10B trials of tenecteplase and reteplase treatment of acute myocardial infarction. WBC count was obtained at entry, before drug administration. Higher WBC counts were associated with resistance to thrombolysis, increased thrombus burden, and impaired microvascular perfusion. 30 day mortality was 10.4% in patients with WBC count >15 000/mm^3 and 0% in patients with WBC count was 5000/mm^3, and a similar difference was noted for the development of congestive heart failure or shock. Barron et al concluded that an elevated leukocyte count was associated with a poorer response[43]

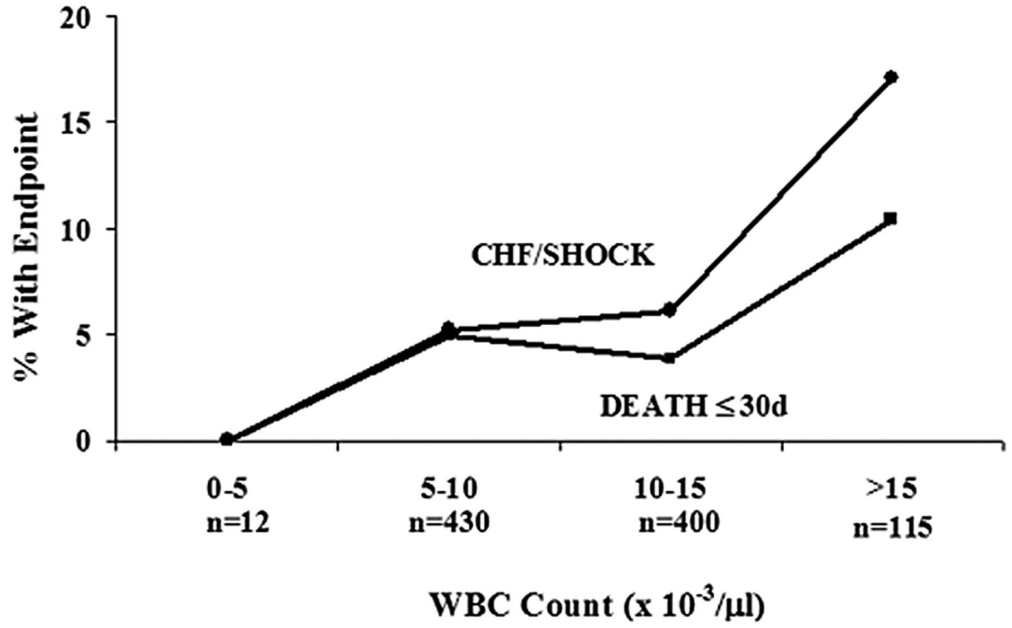


Figure 9. Association between WBC count and development within 30 days of death or either congestive heart failure (CHF) or shock in 975 patients in the TIMI 10A and 10B trial.[43]

to therapy and not just a larger infarct at presentation. This was true even after adjusting for other risk factors like admission TIMI flow, myocardial perfusion grades, anterior myocardial infarction location, baseline and maximum creatinine kinase (CK) levels and smoking status. Thus, WBC count demonstrated a strong trend toward an independent association with the development of new congestive heart failure and death (odds ratio, 1.21; P=0.07) (Figure 9).[43]

Differential leukocyte count as a risk factor and prognostic indicator:

Most studies of the association of leukocytosis and ischemic vascular disease recorded a total WBC count without a leukocyte differential analysis, and thus, there are relatively few data on the specific cell type most associated with the increased risk. In the CAPRIE study, elevations in neutrophils and to a lesser extent monocytes showed significant associations with the risk of recurrent ischemic events, but elevations in lymphocyte count showed, if anything, an inverse relationship to the risk of recurrent events.[71] In the Evaluation of c7E3 for Prevention of Ischemic Complications (EPIC) study, the total WBC count correlated best with 3-year mortality, but the neutrophil count also showed a correlation.[72] The monocyte count was not correlated with outcome, and as in the CAPRIE study, the lymphocyte count demonstrated an inverse relationship. Among the

leukocytes, morbidity and mortality is most closely associated with the neutrophil count. Monocyte production of tissue factor is well established and can be enhanced by activation, providing a direct link to thrombosis; the importance of neutrophils as a source of tissue factor is less certain.[47] It is notable that an inverse relationship between mortality and lymphocyte count was observed, even though the relationship was not as strong as the direct associations involving total WBC count and neutrophils. Because lymphocyte count are depressed by elevated glucocorticoid levels, even during the diurnal cycle,[48] it is possible that the lower lymphocyte count in patients with a poorer prognosis reflect elevated glucocorticoid levels. In fact, relative lymphocytopenia in patients with chest pain was found to be similar to rapid creatinine kinase-MB in diagnosing a myocardial infarction (sensitivities of 58% and 56% for lymphocytopenia and elevated rapid creatinine kinase-MB, respectively; specificities of 91% and 93%); elevated cortisol levels were found in this same group of patients (diagnostic sensitivity of 68% and specificity of 86%). Acanfora et al.[73] evaluated the relationship between lymphocyte count and end points of total mortality and cardiovascular mortality. The three-year mortality rate was found to be 64% in persons with a lymphocyte count 20% versus 40% in those with a lymphocyte count of $\geq$20% ($p = 0.0001$). The multivariate adjusted hazard ratio of mortality was found to be 1.73 (95% confidence interval (CI) 1.21 to 2.48, $p = 0.0026$).

In the Hiroshima and Nagasaki Adult Health Study[49] the total leukocyte count correlated positively with the incidence of CAD in a large population of individuals free of disease at baseline. When differential cell count were considered, a correlation was found between moderately elevated eosinophil count and increased risk of disease, as well as between neutrophil, eosinophil, and monocyte (but not lymphocyte) count and the incidence of disease. The Paris Prospective Study II[50] revealed that, after adjustment for other variables, the risk of CAD increased 1.15 times for each increase of 100cells/mm^3 in monocyte count. Prospective studies have shown that the inflammatory cell activity and leukocyte count may be useful prognostic indicators in patients with acute MI or UA. In a one-year follow-up study of patients with UA,[51] patients who had the highest leukocyte count were roughly eight times more likely to have a major cardiovascular event than patients with the lowest count and were five times more likely to have one than all other patients.

Leukocytes and other risk factors of CAD : The associations between leukocyte count and other risk factors for CAD, especially smoking, have been evaluated in a number of studies. The leukocyte count has been shown to correlate positively with cigarette smoking, serum total cholesterol, serum triglycerides, clotting factors, hematocrit, fasting glucose levels, and diastolic blood pressure and inversely with serum high-density lipoprotein

cholesterol, forced expiratory volume, forced vital capacity, and height. The interdependence of leukocyte count and smoking remains unclear, as the WBC count is usually higher in smokers. However, the WBC count has been shown to be an independent predictor of CAD in multivariate analyses adjusting for other risk factors, including smoking in different population.[52]

The strong association between cigarette smoking and elevated leukocyte count has been documented in many studies and even regular exposure to "second hand" smoke is associated with increased leukocyte count.[54,55] There is increasing evidence suggesting a relationship between obesity and inflammation. A higher BMI is associated with higher serum C-reactive protein (CRP) concentrations in both children and adults suggest a state of low-grade systemic inflammation in overweight and obese persons. Kullo et al. showed that persons with a BMI $\geq$30 kg/m^2 had a higher WBC count than those with a BMI <25 kg/m^2 (WBC count = 5.86 vs. 5.26 x 10^9/l, respectively; $p < 0.05$). Huang et al.[56] reported a positive and significant relationship between the total WBC, neutrophil, lymphocyte, and monocyte count with smoking and BMI ($p < 0.001$).

Two case-control studies in disease-free subjects[57,58] confirmed the correlation between leukocyte count and CAD. One of these studies,[59] which evaluated gender-, age, and risk-matched subjects, found that the mean leukocyte count was higher in patients than in control subjects (8,000/mm^3 vs. 7,500/mm^3). The other study, which used a cohort of dyslipidemic men from the Helsinki Heart Study of coronary atherosclerosis primary prevention, found leukocyte count to be higher in patients than in controls at baseline before admission. In addition, smokers with elevated white blood cell (WBC) count had a higher relative risk for disease than non-smokers. As discussed later, the WBC count is usually higher in smokers; however, their effect is mostly additive, as WBC is an independent risk factor for CAD. Retrospective studies in disease-free subjects have also correlated the leukocyte count and CAD. A large, retrospective five-year cohort study [60] showed not only that high leukocyte

count at baseline correlated with the development of acute coronary syndromes, but also that baseline leukocyte count were higher in diseased patients than in patients who had no significant CAD. The most important questions are: 1) Which leukocyte count cutoff points will be most useful for predicting CAD risk in clinical practice? 2) What is the relative predictive value of differential leukocyte count? Which leukocyte subtype or subtypes (eosinophils, basophils, or neutrophils), if any, will be most useful for predicting risk? 3) Will combining serum markers of inflammation (such as CRP, lipoprotein phospholipase A_2, pregnancy-associated plasma protein-A, and myeloperoxidase) with the leukocyte count increase predictive ability?

SUMMARY: Atherosclerosis is a multifactorial disease with dyslipdemia, hyperglycemia, smoking and other causes of endothelial injury and genetic predisposition, all contributing to pathogenesis. In recent years it has been recognized that atherogenesis represents an active inflammatory process rather than simply passive injury with infiltration of lipids. The white cell count has been proposed as a biomarker for cardiovascular risk prediction. Among the inflammatory markers C-reactive protein has been extensively studied and clinically applied for risk stratification in CAD. However its value as a predictor of cardiovascular risk been questioned recently. Hence, the need to develop and apply additional complementary inflammatory markers of cardiovascular risk. The WBC count provides an assessment of inflammatory status. This inexpensive and universally obtained test has not been fully explored or exploited for its predictive ability.

Materials & Methods

Study population:

We recruited 118 patients with acute myocardial infarction, admitted in the Department of Cardiology, Christian Medical College, Vellore, between August 2004 to June 2006.

Base line assessment:

A detailed medical history regarding risk factors like-diabetes mellitus, hypertension, smoking, obesity, dyslipidemia and family history of premature coronary artery disease; as well as previous symptoms such as preinfarction angina were obtained. Full physical examination was done in all patients. Killips score in acute MI on hospital admission, BMI, total and differential WBC count, serum creatinine level were obtained. Serum level of hs CRP was measured at admission in all patients. Any evidence of the presence of an obvious source of infection, either by clinical assessment or laboratory investigations served as basis for exclusion from the study.

Definitions and Data Collection :

Acute ST segment elevation myocardial infarction was defined as typical chest pain with ST-segment elevation at J point in >2 contiguous leads, with a cutt off >0.2mV in V1, V2 or V3 or >0.1mV in other leads. Body mass index (BMI) was defined as the weight in kilograms divided by the square of the height in meters. Detailed in-hospital data were obtained regarding all adverse events.

Inclusion criteria :

- All Patients presenting to the hospital with ST elevation myocardial infarction.

1Exclusion criteria :

1 • Patients with other systemic illnesses where CRP is elevated (infections,

0 chronic Inflammatory diseases like – Rheumatoid arthritis etc.)

2 • Patients with malignancies

3 • Patients who had recent surgery / trauma

Echocardiographic studies :

Echocardiographic measurements were obtained by using the HP Sonos 5500 echocardiography machine on the first or second day of admission. Left ventricular end diastolic volume, end systolic volume and ejection fraction, were assessed from the apical four-chamber view using Simpson's rule. Regional wall motion abnormalities were also documented.

Laboratory methods of measuring hs-CRP and WBC count :

hs-CRP was measured on the Immulite 2000(DPC) by a chemiluminiscent immuno assay. CRP in each serum sample is captured by a ligand labeled anti CRP murine monoclonal antibody. The detection antibody is rabbit polyclonal anti CRP tagged with alkaline phosphatase. The entire complex is bound by antiligand on a polystyrene bead. Alkaline Phosphatase acts on the chemoluminescent substrate producing dioxetone which releases photons and is measured as light units which is directly proportional to the concentration of CRP.

The WBC count was measured using a standard technique and expressed as absolute count per mm^3. WBC count was analyzed using Beckman Coulter equipment.

Post MI complications

The following variables were taken for the purpose of post MI complications:

1. Post infarction angina
2. Cardiogenic shock

3. Mitral regurgitation
4. Left Ventricular failure (LVF)
5. Complete heart block
6. Arrhythmias/ LBBB/RBBB/LAHB/LPHB
7. Pericarditis
8. Cardiac rupture
9. Re- infarction
10. Mortality
11. Non-cardiac complications such as CVA.

Statistics :

All continuous variables were expressed as mean and standard deviation; whereas categorical variables were expressed as numbers with percentages. For univariate analysis, categorical variables were compared by using chi-square test or Fisher's exact test (where the numbers were small). Multivariate analysis was performed using logistic regression. Receiver operator characteristic curves were plotted to obtain best cut off points. Statistical significance was defined as a value of $p < 0.05$. All computations were performed using SPSS 13.0 software, Chicago, Inc.

Results

Of the 118 patients, 102 were men and 16 were women. The age of these patients was 56.06 ± 12.12 (range 27-96 years). Hypertension was present in 65 patients, diabetes in 69 patients. 106 of the 118 patients had thrombolysis (89.9%). Seven patients underwent primary PTCA, all subjects were men; 5 (4.9%) patients were not thrombolysed because of late presentation and advanced age. Eleven patients underwent rescue PTCA (10 male & 1 female) (Table 1). Out of those who underwent cardiac catheterization, 5 (29.4%) patients had single vessel disease, 9 (52.9%) had double vessel disease and 3 (17.6%) had triple vessel disease. 83 patients (69.2%) had LVEF <50% and 37 (30.8%) had LVEF ≥50%.

Table 1. Baseline clinical characteristics

We measured hs-CRP level and white cell count on the date of admission. The hs CRP was 5.35 ± 6.5mg/dL, the CKMB was 71.7 ± 77.1 IU/L, serum creatinine was 1.13 ± 0.3mg%, and the WBC count was 13309.32 ± 3708count /mm^3. Differential count results are as follows neutrophils 72.42 ± 12.3%, lymphocytes 20 ± 9.9%, monocytes 4.42 ± 2.82%,

basophils 0.25 ± 0.45%, and eosinophils 1.48 ± 1.8% (Table 2).

Table 2. Baseline Laboratory Findings

Variables	
CKMB (IU/L)	71.7 ± 77.1
hs-CRP (mg/dL)	5.35 ± 6.5
WBC count (cells/ mm^3)	13309 ± 3708.6
Neutrophils%	72.4 ± 12.3
Lymphocyte %	20 ± 9.9
Monocyte %	4.42 ± 2.82
Basophil %	0.25 ± 0.45
Eosinophil %	1.48 ± 1.8

The average hospital stay was 4.5 ± 2.0 days. Six patients developed cardiogenic shock, one recovered, five patients expired. In total eleven patients expired during hospital course; eight patients expired within 48 hours of admission. Sixty-nine (58.5%) patients were discharged uneventfully. Details of post MI complications are listed in table 3 and figure 1.

Table 3. Frequency And Percentage Of Occurrence Of

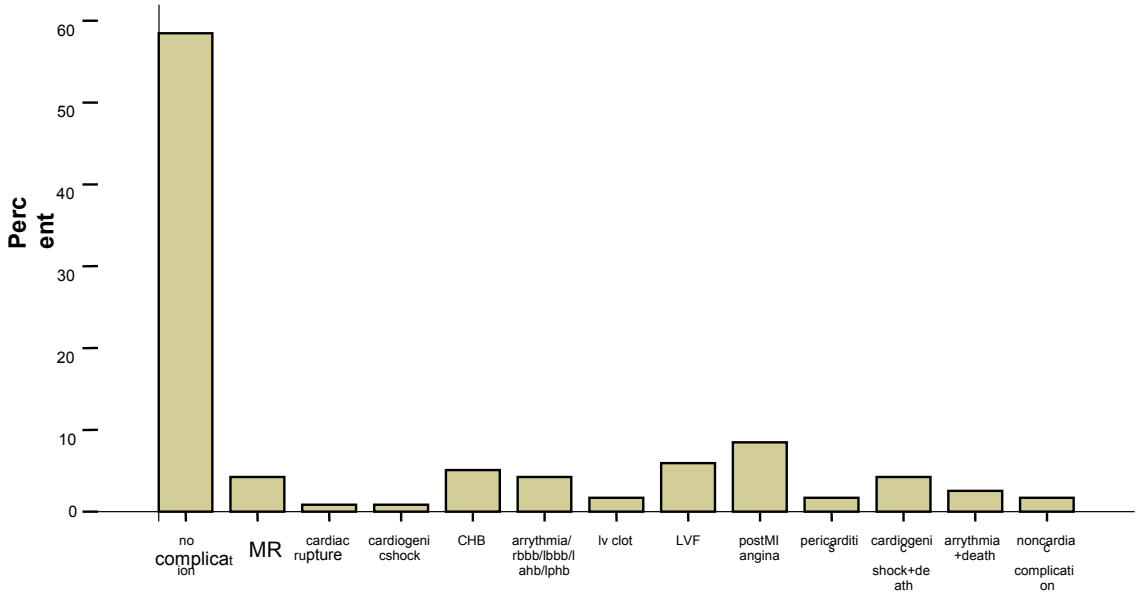
The Various Post MI Complications

Post MI complications	Frequency	Percentage
Mitral regurgitation	5	4.2
Complete heart block	6	5.1
Cardiac rupture	1	0.8
Cardiogenic shock +recovered	1	0.8
Arrhythmia /LBBB/RBBB	5	4.2

Post MI angina ± reinfarction	10	8.5
Pericarditis	2	1.7
Left ventricular failure ± reinfarction	7	5.9
LV thrombus	2	1.7
Cardiogenic shock +death	5	4.2
Arrythmia(VT+VF)+death	2	2.5
Non cardiac complication	2	1.7

The presence of any complication after the acute myocardial infarction was taken as the outcome. Complications occurred overall in 41.5% of patients. The most common complication was post infarction angina, which preceded most of other complications. In total 11(9.3%) patients expired during hospital course; eight patient expired within 48 hours of admission. Most common cause of death was cardiogenic shock (Table 3 and Figure 1).

Figure 1: Bar diagram showing Post MI complications



We looked at the post MI complications in relation to the site of myocardial infarction

(Table 4). There were 70 patients with anterior wall MI and 48 patients with non-anterior wall MI (including inferior, posterior and right ventricle MI) respectively. Predominantly anterior wall MI patients (n=33, 71.7%) had more post MI complications compared to non AWMI (n=13, 28.3%)(p =0.028, as analyzed by chi square test) (Table 4).

Table 4. Post MI Complications Analyzed By the Site of Myocardial

	Anterior wall MI n =70	**Non-anterior wall MI n =48**	**P Value**
Post MI complications n(%)	33(77.7)	13(28.3)	0.028

We looked at the presence of an association between the various baseline risk factors and the occurrence of post MI complications. The window period of presentation, killips class at admission, LV dysfunction, hs-CRP level, total WBC

Table 5. Univariate Analysis Assessing Post MI Complications

By Baseline Features And Various Risk Factors*

	Without Post MI complications	**With Post MI complications**	**p Value**
Window period(hrs) < 3 3 - 6 > 6	 12(75) 44(66.7) 16(44.4)	 4(25) 22((33.3) 20(55.6)	*0.042*
Killip class I II III IV	 44(80) 26(55) 2(15.4) 0(0)	 11(20) 21(44.8) 11(84.6) 3 (100)	*0.001*
AWMI Non AWMI	 37(51.4} 35(48.6)	 33(71.7} 13(28.3)	*0.028*

LVEF% < 50 ≥ 50	 48(56.2) 30(83.3)	 40(48.8) 6(16.7)	 *0.001*
CKMB IU/L <25 ≥ 25	 26(68.4%) 46(57.5%)	 12(31.6) 34(42.5)	 *0.25*
HsCRP mg% < 3 ≥ 3	 50 23	 12 35	 *<0.001*
LDL mg% < 100 ≥ 100	 27(62) 44(64)	 16(37) 24(35)	 *0.838*
hsCRPmg%+LDL mg% *<3 + <100* *≧ 3 + <100* *< 3 + ≧ 100* *≥ 3 + ≧100*	 *22(73}* *6(35.3)* *26(86.7)* *18(61)*	 *8(26.7)* *11(64.7)* *4(13.1)* *23(56)*	 *<0.001*

*Values given as n. (%).

count, and neutrophil & lymphocyte percentage in the differential count were found to be significant in univariate analysis. LDL level by itself did not have a significant correlation (Table 5, 6, 7 & 8).

Table 6. Association Between hs-CRP And Post MI Complications

hs-CRP mg/dL	Post MI complications (n)	p Value
<3	12	0.001
≥3	34	

We analyzed post infarction complications in relation to quartiles of hs-CRP level (Figure.7)

Table 7. Post MI Complications During Hospital Course

By Quartiles Of hs-CRP Levels

Post MI complications	Quartiles of hs- CRP (mg %)			
	<1.13	1.13 - 2.7	>2.7 - 7.2	>7.2
Mitral regurgitation	2	1	2	0
Complete heart block	2	0	4	0
Cardiac rupture	0	0	0	1
Cardiogenic shock +recovered	1	0	0	0
Arrhythmia /LBBB/RBBB	1	0	2	2
Post MI angina ± reinfarction	1	1	2	8
Pericarditis	0	0	1	1
LVF ± reinfarction	0	2	0	5
LV thrombus	1	0	1	0
Cardiogenic shock ± reinfarction +death	1	0	1	3
Arrythmia(VT+VF)+death	0	0	2	1
Non cardiac complication	1	1	0	0

* Values given as n

We looked at post MI complications stratified by total and differential WBC count as shown in table 8. As seen, there is a significant association between the post MI

complications and total WBC count, as well as neutrophil and lymphocyte count.

Table 8. Univariate Analysis Assessing Post MI Complications By WBC And Differential Count *

	With Post MI complications	Without Post MI complications	p Value
WBC count/mm ^{3}			
5001to10000	16 (72)	6 (27.3)	0.005
>10001 to15000	43 (69.4)	19 (30.6)	
> 15000	13 (38.2)	21 (61.8)	
Neutrophil Bandforms	24 (54.3)	20 (45.5)	0.266
Neutrophil %			
<65	25 (80.6)	6 (19.4)	0.003
66-75	27 (65.9)	14 (34.1)	
>75	20 (43.5)	26 (56.5)	
Lymphocyte %			
<14	16 (43.3)	21 (56.8)	
14-20	17 (63)	10 (37)	0.017
21-24	16 (61.5)	10 (38.5)	
>24	23 (82.1)	5 (17.9)	

*Values given as n. (%).

We also analyzed post infarction complications in relation to white cell count in various groups (Table 9).

Table 9. Post MI Complications In Relation To Leukocyte Count

Post MI complications	WBC count/mm^3		
	5000 to 10000	10000 to 15000	>15000
Mitral regurgitation	0	4	1
Complete heart block	2	1	3
Cardiac rupture	0	1	3
Cardiogenic shock + recovered	0	0	1
Arrhythmia /LBBB/RBBB	0	3	2
Post MI angina ± reinfarction	1	4	5
Pericarditis	0	2	0
Left ventricular failure ± reinfarction	1	1	5
LV thrombus	1	0	1
Cardiogenic shock + death	1	2	2
Arrhythmia(VT+ VF) + death	0	2	1
Non cardiac complication	2	0	0

*Values given as n.

The presence of any association between various traditional risk factors and CRP level was determined by Chi Square and Fisher's exact tests where applicable. The factors that were significantly associated with hs-CRP level more than 3 mg/dl were window period in hours and post MI complications (Table 10).

Table 10. Relationship Between Risk Factors And hs-CRP Level*

	hs-CRP<3mg/dl n=61	**hs-CRP≥3mg/dl n=57**	**P Value**
Male/female	54/7(52.5/43.8)	48/9(97.1/56.3)	0.49
Age <55/>55yrs	31/30(52.5/50.8)	28/29(47.5/49.2)	0.72
HTN	35 (53.9)	30 (43.5)	0.60
DM	39 (53)	3043.5)	0.22
Dyslipidemia	25(41)	47	0.09
Smoker	31	28	0.85
BMI ≥25kg/m^2	36 (59)	48(75.9)	0.05
Window period (hrs) in 3 category <3/>6 3to6/>6 <3/ 3-6	 14(23) 34(55) 13(21.3)	 2(3.5) 32(56) 23(40.4)	0.003
Killips Class I II III IV	33(54) 23(37.7) 5(8.2) 0(0)	22(38.6) 24(48) 8(14) 3(5.3)	0.123
AWMI	34(55.7)	36(63.2%)	0.412
TC >200mg%	16(26.7)	15(28%)	0.79
LDL 100mg%	29(49.2)	14(26.9)	0.016
HDL<40 mg%	39(65)	25(48)	0.07
TGL >150mg%	34(55.7)	27((51)	0.06
Post MI complications	12(19.7)	34(59.6)	0.0001

* Values given as n. (%).

In univariate analysis, LVEF <50% was significantly associated with a high level of hs-CRP (Table 11).

Table 11. Univariate Analysis Of Echocardiographic Parameters With hs-CRP

We also analyzed the LV systolic function in relation to hs-CRP and WBC count. Table 12 shows the significant inverse correlation between hs-CRP level and WBC count with occurrence of LV dysfunction.

Table 12.Univariate Analysis of LV EF with hs-CRP and WBC

	LV EF <50%	LV EF ≥50%	P Value
hs-CRP mg%			
< 3	35(42.7)	47(57.3)	0.003
≥3	22(72.2)	10(27)	
WBC Count /mm^3			
<10000	10(12.2)	12(33.3)	0.002
10000 -15000	45(54.9)	17(47.2)	
>15000	27(32.9)	7(7(17.4)	
hs-CRPmg% + WBC/mm^3			
<3 + <10000	3(3.7)	9(25%)	<0.001 (Fisher's exact test)
<3 + >10000	28(34.1)	16(44.48%)	
>3 + <10000	17(20.7)	5(13.3%)	
>3 + >10000	34(41.5)	6(16.7%}	
hs-CRP mg% + LDL mg%			
<3 + <100	20(66.7}	0(33.3)	<0.001 (Fisher's exact test)
≥3 + <100	12(70.6)	5(29.4)	
<3 + > 100	13(43.3)	17(56.7)	
≥3 + >100	37(90.2)	4(9.8)	
LDL mg%			
<100	27(36)	18(44)	0.28
>100	48(69)	20(55)	

*Values given as n. (%).

We looked at the presence of an association between the various risk factors and the occurrence of any post MI complications. Gender, total WBC count (stratified as 5000 to 10000; 10000 to 15000; >15000 cells/mm^3), hs-CRP level (<3mg% &≥3mg%) and LV EF (<50%& ≥ 50%) had a significant association by multivariate analysis (Table 5). Traditional risk factors such as diabetes, hypertension and smoking were not of significance in predicting occurrence of post MI complications. Multivariate analysis using logistic regression was done to analyze the significance of various risk factors in the occurrence of post MI complication.

The following table shows the odds ratio (OR) and 95% confidence intervals(CI). The odds ratio of a hs-CRP level of ≥ 3 mg/dl for post MI complications was 5.2 (95% CI: 2.0 to 13.7) and odds ratio of a white cell count of >15000 cells/mm^3 for post MI complications was 2.7 (95%CI: 1.2 to 5.7) (Table 13)

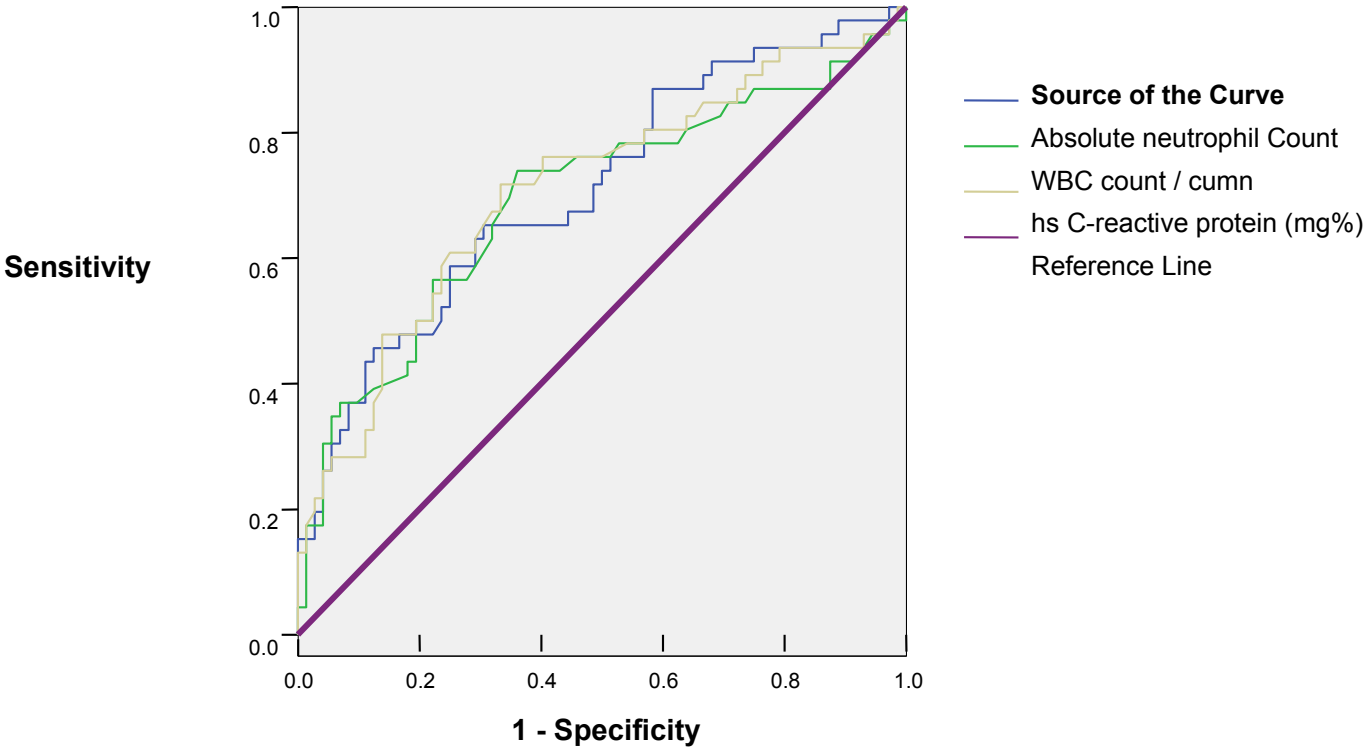
Table 13. Logistic Regression Analyzing Post MI Complications By Various Risk Factors

		B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I.for EXP(B) Lower	Upper
Step a 1	Sex				1				
	Age				1				
	BMI				1				
	HTN				1				
	Diabetes				1		1.567		
	Smoker				1				
	Srcreatinine				1				
	Dyslipcdemi				1				
	LVEF%				1				
	WBC				1				
	Hs-CRP				1				
	Constant	-9 956	2 965	11 271	1	001	000		

a. Variable(s) entered on step 1: sex, Age,BMI, HTN, Diabetes, smoker, srcreatinine, dyslipcdemia LVEFWBC hsCRP

ROC curves were plotted with hs-CRP, total WBC count, absolute neutrophil and lymphocyte count against presence or absence of post MI complications in order to determine the relationship of these risk factors with the outcome measure and find out best cut off points which predict the occurrence of complications with optimal sensitivity and specificity (Figure 2, 3 & Table 13).

Figure 2. ROC Curve Plotted with hs-CRP, total WBC count and absolute neutrophil count against Post MI complications



Diagonal segments are produced by ties.

Table 14. Best Cut Off Points Obtained From The ROC Curves To Predict Occurrence Of Post MI Complications

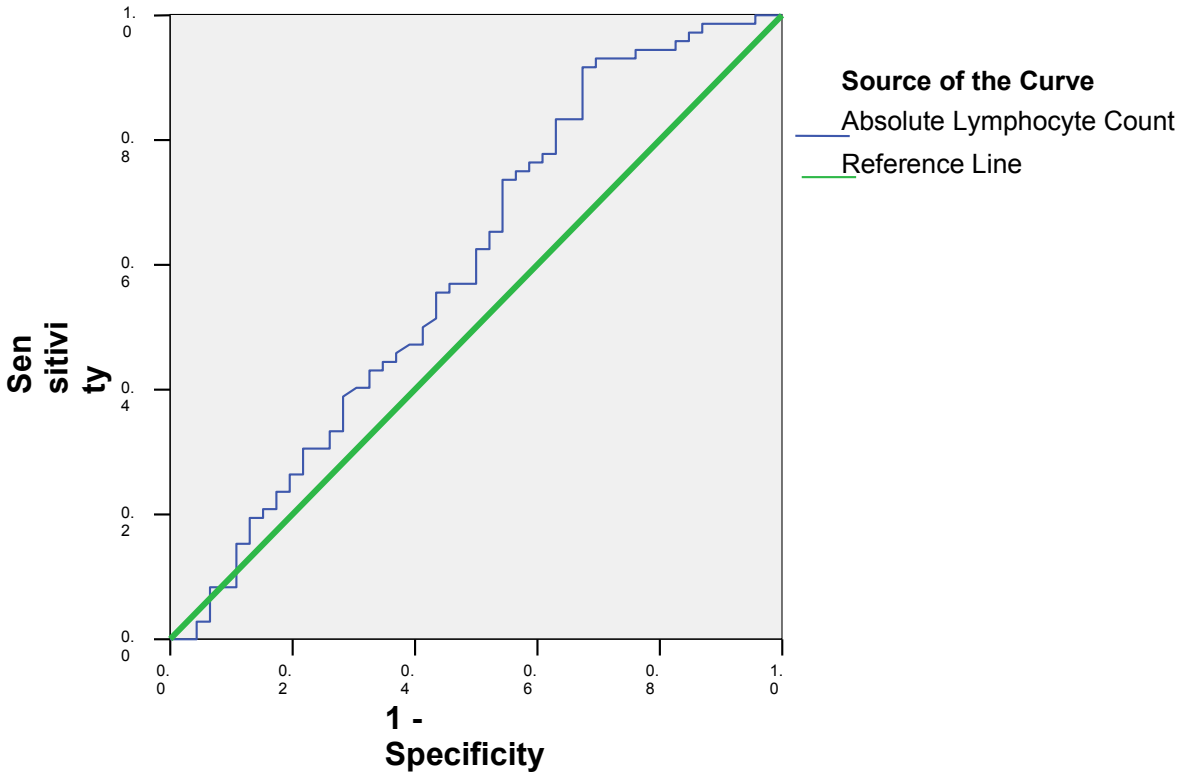
Variable	Cut off point	Sensitivity%	Specificity%
hs-CRP mg%	2.9	65.3	71.7
WBC Count/mm^3	12,950	73.5	63.9
Neutrophil count/mm^3	9,720	65.2	69.4

For the lymphocyte count, it was observed that a lower lymphocyte count, to predict

greater occurrence of post MI complications, i.e., the relationship was inverse. Hence a curve-taking non-occurrence of complications as the outcome was plotted (Figure 3).

By the ROC curve, the cut off point for the absolute lymphocyte count below which post MI complications would be predicted to be 1530 cells/mm^3 with a sensitivity of 91.7% and specificity of 43% (Figure 3).

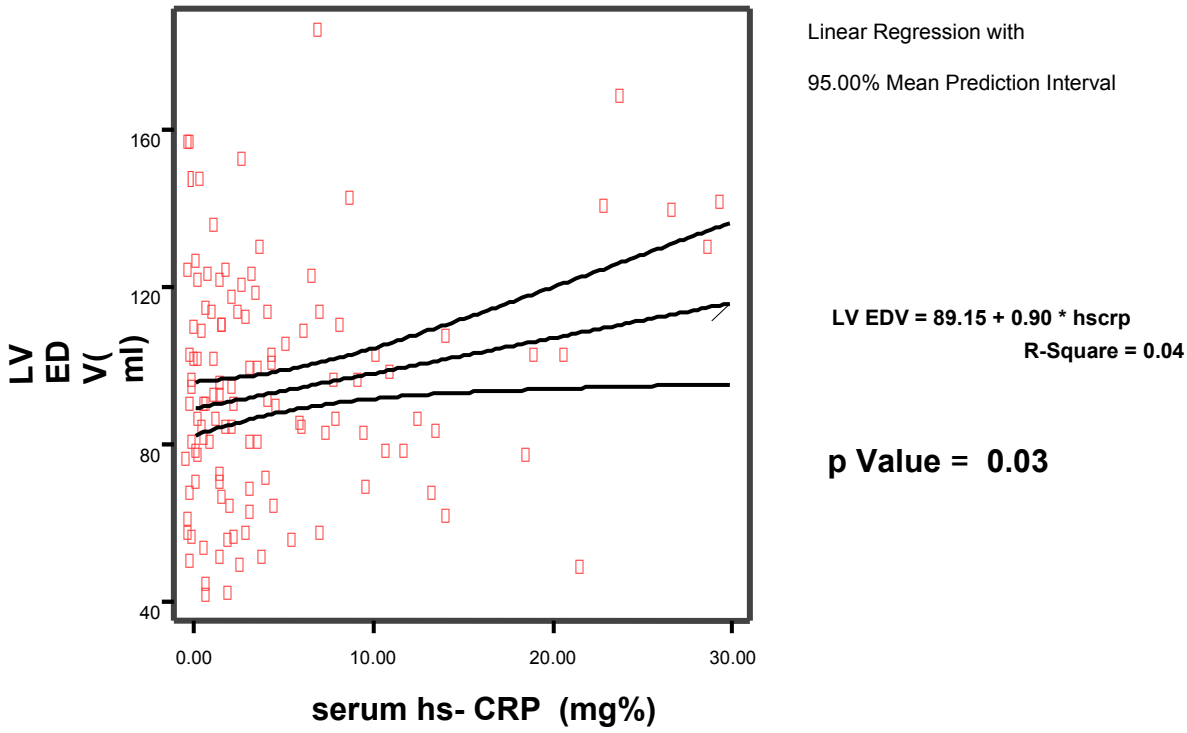
Figure 3. ROC Curve Plotted With Absolute Lymphocyte Count Taking Against Non occurrence of Post MI Complications as outcome



Diagonal segments are produced by ties.

We analyzed parameters of ventricular systolic performance namely LVEF (%) and LVEDV (ml) in relation to hs-CRP. As the scatter plots demonstrate, a significant linear correlation exists between hs-CRP and these parameters. Figure 4 shows that hs-CRP levels correlate positively with LV end diastolic volume.

Figure 4. Scatter Plot Showing The Association Between hs-CRP And LV End Diastolic Volume



The next scatter plot demonstrates that hs-CRP level correlates inversely with left ventricular ejection fraction (LVEF) (Figure 5).

Figure 5. Scatter Plot Showing A Correlation Between hs-CRP And LV Ejection Fraction (LV EF%)

Discussion

Our study shows a significant association between hs-CRP levels and total WBC count at admission to the in-hospital complications observed in STEMI patients.

Of the total 118 patients, complications occurred in 42% of the patients; 11 deaths (9.3%) occurred in the hospital course. The most common post MI complication was post infarction angina and most common cause of mortality was cardiogenic shock.

In our study, a high hs-CRP level (≥ 3 mg/dL), was shown to be significantly associated with post MI complications during hospital course, such as post infarction angina, mitral regurgitation, complete heart block, left ventricular failure and mortality etc., odds ratio was 5.2 (95% CI:2.0-13.7; p<0.001). Our results are in agreement with O Keskins et al [61] and partially with Suleiman et al [62] who collected blood samples at the time of admission, within 6-12 hrs and 12-24 hrs respectively. O Keskins et al [61] reported that high hs-CRP (>2.0mg%), collected once at admission was an independent predictor of 30 day recurrent cardiac events, such as reinfarction, post MI angina and cardiac death, the odds ratio was 1.024 (95% CI:1.002–1.047;P <0.03). Suleiman et al [16] reported that a high CRP level (>2.23mg%) obtained within 12-24 hours of symptom onset, was an independent predictor of 30 day mortality and heart failure, relative risk was 3.0 (95% CI:1.3-7.2), but not associated significantly with the development of post infarction angina or recurrent myocardial infarction in patients with acute myocardial infarction. Zebrack et al [63] reported that CRP level, collected in acute myocardial infarction patients at predischarge was not associated with the death or recurrent cardiac events (Table15).

Table 15. hs-CRP level and odds ratios for post MI complications

Study	hs-CRP level	RR/OR	95% CI
OKeskins et al [61]	>2.0 mg% (once at admission within 6-12 hrs)	1.024 for recurrent cardiac events within 30 days	1.002 to 1.047
Suleiman et al [62]	>2.23 mg% (once at admission) within 12 -24hrs	3.0 for 30 d mortality and heart failure	1.3 to 7.2
Anzai et al [35]	>20 mg% (peak)	4.72 for cardiac rupture & one year cardiac death	1.6 to 13.6
Zebracks et al [63]	CRP levels, at predischarge	Not associated with death or recurrent cardiac events	
Helsinki Heart Study	Highest quartile	3.56; for risk of MI or death	1.93 to 6.3
Our study	≥ 3 mg% (once at admission) within 6 to 12hrs	5.2 for post MI complications during hospital course	2.2 to 13.7

The importance of an elevated leukocyte count in the setting of acute coronary events has been described from very early times. A high WBC count has been shown to increase the risk of developing MI and increased post MI adverse events.[74]

Table 16. White Cell Count And Relative Risk / Odds Ratios

For Post MI Complications

Study	WBC count / mm^3	RR/OR	95% CI
Furmans et al [64]	Uppermost quintile	1.7	1.14 to 2.58
OKeskins et al [61]	>14000 at admission within 6-12hrs	1.013	0.9 to 1.0
Barron et al [38] (TIMI) 10A and 10B trials	>15000 within 24 hrs	10.2% 30 days mortality	
Cole et al [35]	>15000	32% of with MI died within 2 months	
NRMI [37]	Fourth versus first quartile	2.71	2.53 to 2.9
Our study	>12900 at admission within 6 hrs	2.7	1.2 to 5.7

Epidemiologic studies have demonstrated correlations between the WBC count and the risk of acute myocardial infarction and stroke. The risk of AMI or death is approximately four times greater in persons with WBC count high in the normal range (>9,000 cells/mm^3) than in persons with WBC count low in the normal range (<6,000 cells/mm^3). A high WBC count also predicts a greater risk of re-infarction and of in-hospital death. Cole et al [46] reported

that the risk of death within 2 months in patients with acute myocardial infarction was four times greater in those with WBC count higher (> 15,000 cells/mm^3) than those with normal WBC count (<10,000 cells/$mm^{3)}$. Furmans et al [64] examined the relationship between WBC and short-term prognosis following AMI, and found that patients in the uppermost quintiles of WBC were more likely to have a complicated hospital course and more extensive acute myocardial necrosis. The adjusted odds ratio (OR) four versus the first WBC quartile in National registry in myocardial infarction was remained significant with in-hospital mortality among entire population (OR: 2.71[95%CI: 2.53 to 2.73]). [37]

In the study by Barron et al, [38] he found that WBC count within 24 h of admission for an AMI is a strong and independent predictor of in-hospital and 30-day mortality as well as in-hospital clinical events. Some studies have not found correlation between high leukocyte count and complications following acute coronary syndromes. O Keskins et al [61] found that WBC count was not an independent prognostic predictor for post MI complications, however they reported a strong correlation between WBC count, post MI complications and between WBC count and CRP levels overall (Table 16).

Our study has shown that a high WBC count was significantly associated with post MI complications even after adjustment for other potential confounding factors such as age, diabetes, hypertension, smoking and hs-CRP level. It was found to be a strong independent predictor of post MI complications such as post infarction angina, LV dysfunction. We also analyzed outcome by differential leukocyte count, which has been a potential limitation in previous epidemiologic studies. [38, 46,61,64,65] In our study, high neutrophil and low lymphocyte percentages were found to be significantly correlated with post MI complications.

We also looked at the best cut off points for hs-CRP level, total WBC count, absolute neutrophil (ANC) and lymphocyte count (ALC) in the prediction of post MI complications, by plotting the receiver operator characteristic curve. The best cut off point of CRP was found to

be 2.9 mg/dL with a sensitivity of 71.7% and specificity of 65.3%. The cut off for total WBC, ANC and ALC were 12,950 cells/mm^3, 9720 cells/mm^3 and l530 cells/mm^3 respectively with sensitivities of 73.5%, 65.2%, 91.7% and specificities of 63.9%, 69.4% and 43% respectively. As there is considerable interest in developing hs-CRP as a prognostic tool in the setting of acute MI, these cut off values could be useful in risk stratification. These correlations possibly reflect that coronary inflammation is an ongoing process during AMI. Thus, inflammatory markers, such as CRP level, WBC count and its differential count can be used to predict short-term prognosis in patients with AMI.

Conclusions

1. In patients presenting with acute ST segment elevation myocardial infarction, elevated hs-CRP level was associated with significant in- hospital complications (odds ratio = 5.2 [95% CI:2.0-13.7]).

2. The neutrophil and lymphocyte counts individually were also found to have a significant correlation with post MI complications. By the ROC curve, the ideal cut off point for total WBC count to predict post MI adverse events was found to be 12,950 cells/mm^3 with sensitivity of 73.5% and specificity of 63.9%. The best cut off point for the absolute neutrophil count to predict post MI complications was 9,720 cells/mm^3 with sensitivity of 65.2% and specificity of 69.4%.

3. Our results suggest that hs-CRP level and white cell count obtained at admission in acute ST segment elevation myocardial infarction can be used as a marker for identification of patients who are likely to develop significant complications in the hospital course.

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Abbreviations & Acronyms

CAD	-	Coronary artery disease
HTN	-	Hypertension
DM	-	Diabetes mellitus
BMI	-	Body mass index
STEMI	-	ST-segment elevation myocardial infarction
AMI	-	Acute myocardial infarction
LV EF	-	Ejection fraction of left ventricle
LDL	-	Low-density lipoprotein
HDL	-	High-density lipoprotein
hs CRP	-	High sensitivity C- reactive protein
LVEDV	-	Left ventricle end diastolic volume
WBC	-	White blood cell count
ALC	-	Absolute lymphocyte count
ANC	-	Absolute neutrophils count

APPENDIX

STUDY PROFORMA

HIGH-SENSITIVITY C-REACTIVE PROTEIN, LEUKOCYTE AND DIFFERENTIAL COUNT IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Name : Age: Sex: M/F

Hospital No. :

Address :

Height :…….cm Weight :……Kg

Presenting complaint :

Chest Pain / Dyspnea / Syncope

Exclusion criteria :

Fever / connective tissue disorder

Risk Factor :

Hypertension : Yes / No

Diabetes Mellitus : Yes / No

Dyslipidemia : Yes / No

Smoking : Yes / No

Serum cholesterol (mg%)

TC: TG: LDL: HDL:

Admission Killips class : I / II / III / IV

Type of acute myocardial infarction :

Thrombolysis with streptokinase : Yes / No

Primary PTCA : Yes / No

Rescue PTCA : Yes / No

Hospital course and post MI complications : Post infarction angina / LVF / reinfarction / Pericarditis / MR / VSD / Cardiac rupture / Cardiogenic shock

Death : Yes / No Cause of Death :

ECHO : EDV(ml) : EF : %

CKMB(IU/L) :

hs-CRP level (mg%) :

Total WBC count (cells/mm^3):

Neutrophils%: Lymphocytes%: Basophils%:

Monocytes%: Esinophils%: