HIGH TOTAL LEUKOCYTE COUNT AND HEART FAILURE AFTER MYOCARDIAL INFARCTION

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ABSTRACT

Background: Acute myocardial infarction ST-elevation (STEMI) is frequently associated with leukocytosis and relative increased in neutrophil count. It is believed that the peripheral leukocyte count have important prognostic implication in AMI. In this study we hypothesized that there is an association between absolute leukocytosis and neutrophilia to the short term development of congestive heart failure (CHF) after AMI.

Methods: A cross sectional study carried out from June -August 2010. 200 patients with diagnosis of STEMI were included. Patients with a history of chest pain of more than 12 hours, recent trauma, infection, malignancy were excluded.

Baseline demographic data was obtained. Blood sample was drawn for leukocyte count within 12 hours of admission.Echocardiogram (Echo) and X-ray chest was obtained during first four days. Chi square test was applied to seek association between high total leukocyte (TLC) and heart failure.

Results: Out of 200 patients, 98 (49%) remained uncomplicated and they were discharged without clinical evidence of CHF; whereas 91(45.5%) patients who developed clinical CHF underwent Echo and discharged later. Total 11(5.5%) patients expired in hospital. Out of 91 patients who developed CHF 61(67%) had high TLC (>11000 mm^3), while 30 (33%) had normal (<11000 mm3) TLC. Significant association (P<0.008) of high TLC with development of CHF was observed.81 (89%) patients had high neutrophil count (>65 mm^3), while 10 (11%) had normal (≤65 mm^3) Significant association (p < 0.016) of neutrophilia with development of CHF was observed.

Conclusion: This study shows that high TLC count appears to be associated with development of CHF and mortality after acute STEMI.

Keywords: Acute STEMI, congestive heart failure, total Leukocyte count.

INTRODUCTION

Inflammation plays a decisive role in pathophysiology of acute thrombotic events[1]. Inflammation associated with AMI is frequently marked by a peripheral leukocytosis and relative neutrophilia[2]. Elevated counts especially neutrophil count in acute coronary syndromes has been associated with higher risk of acute ischemic events and with adverse angiographic findings.[3]

Whether this process may contribute to the development of post infarction CHF is not established. Heart failure is a frequent and severe complication of acute MI and potent predictor of poor out comes. Its clinical spectrum ranges from mild heart failure to

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cardiogenic shock.[4] High total leukocyte count has been shown to be associated with the development of heart failure in patients with MI.[5] Although the cause of contractile dysfunction may be multifactorial, accumulating evidence suggest that oxidative stress and release of pro-Inflammatory mediators during myocardial ischemia probably contribute to its development.[6,7,8] Inflammatory biomarkers have been identified as an important tool for post myocardial infarction risk stratification.[9,10] Heart failure biomarkers can be categorized empirically as neurohormonal mediators, markers of myocyte injury and remodeling like BNP (Brain Type Natruretic Peptide), PRO -BNP, and indicators of systemic inflammation like CRP, TLC and elevated neutrophil count. Markers of myocyte injury, including troponins, heart-type fatty acide binding protein, and myosin light chain-1, may further improve heart failure prognostication in conjunction with plasma brain natriuretic peptide. Biomarkers of matrix remodeling and inflammation have emerged as potential preclinical indicators to indentify individuals at risk of developing clinical heart failure.[37] The peripheral leukocytes count which provides an assessment of the inflammatory status, and neutrophil count is possibly a markers of intensity of peri-infarction myocardial inflammatory response is an inexpensive and readily available test as compared to C-reactive protein and other acute phase reactants.[11,12,13]

The goal of this study was to assess the utilization of high total leukocytes and neutrophil count as a marker of risk stratification in patient with acute MI for the development of short term post MI heart failure.

METHODS

This was a single centre, cross sectional study, conducted at National institute of Cardiovascular diseases (NICVD), Karachi from June-august 2010. All patients with first presentation of acute STEMI were enrolled. Acute MI is defined as the presence of chest pain and either typical rise and fall of cardiac biochemical markers, or ST elevation in 2 or more contiguous leads at J point or newly developed LBBB. Patients with prior history of infarction, baseline left ventricular dysfunction, known case of cardiomyopathies, chest pain of more than 12 hours were excluded. Similarly, presentation with fever, recent infection with 1 week, history of trauma, malignancy, myeloproliferative disorders, and recent surgical intervention that might have altered the leukocyte count, were excluded.

Informed consent was taken from all patients fulfilling the inclusion criteria. Demographic characteristic, medical history, presenting symptoms, biochemical, electrocardiographic findings, treatment practice during hospitalization, (which were at the discretion of the treating physician of whom were not involved in this study),and in-hospital outcome data, were recorded. A complete physical examination including the assessment of Killip class was carried out and particular attention was given for the evaluation of sign and symptoms of heart failure during admission and subsequently repeated after every 12 hours for the next four days of hospitalization. Four days was chosen as our cutoff because we believed that after this time the development of CHF may be influenced by therapeutic interventions and/or other post infarct complication and therefore that the admission TLC and neutrophil count might be less relevant.

The diagnosis of heart failure was validated by using Framingham criteria as given below[14]. The reliability of ascertaining Framingham HF Criterion in our experience was excellent

Framingham Criteria for Congestive Heart Failure:

Diagnosis of CHF requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria.

Major criteria:

- Paroxysmal nocturnal dyspnea
- Neck vein distention
- Rales
- Radiographic cardiomegaly (increasing heart size on chest radiography)
- Acute pulmonary edema
- S3 gallop
- Increased central venous pressure (>16 cm H2O at right atrium)
- Hepatojugular reflux
- Weight loss >4.5 kg in 5 days in response to treatment

Minor criteria:

- Bilateral ankle edema
- Nocturnal cough
- Dyspnea on ordinary exertion
- Hepatomegaly
- Pleural effusion
- Decrease in vital capacity by one third from ` maximum recorded
- Tachycardia (heart rate>120 beats/min.)

The Framingham Heart Study criteria are 100% sensitive and 78% specific for identifying persons with definite congestive heart failure.

X-ray chest was done on every patient whereas echocardiography was done only on patients with clinical and x-ray findings of CHF due to monetary constraint. LV function and ejection fraction (EF) were estimated by quantitive bi dimensional and bi plane methods from 4 and 2 chamber views and bi dimensional estimated method from multiple echocardiograph views. An EF of < 40 % is considered as a significant evidence of systolic contractile dysfunction. Chest X-ray was graded in three stages as given below;

STAGE 1== Re-distribution of pulmonary vessels.

STAGE 2==Kerly lines, thickened interlobular fissures, peri bronchial cuffing.

STAGE 3== Pleural effusion, bat –wing appearance.

Blood samples were obtained at presentation only. Peripheral leukocyte and neutrophil count was estimated with an automated hematology analyzer. A total leukocyte of > 11000 mm3 and a neutrophil count of > 65% were considered significant.

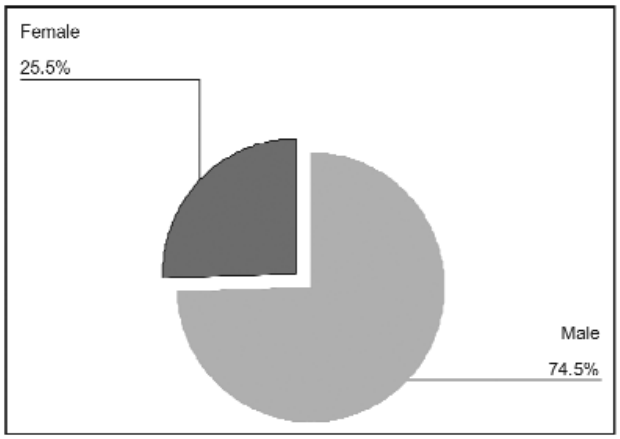
STATISTICAL ANALYSIS

Data analysis was performed through SPSS Version15.Male to female ratio was computed to present gender distribution. Age was presented by mean +_ SD. Frequencies and percentages were computed to present all categorical variables including risk factors, treatment given to patients, high TLC and neutrophil count, and out comes. CHI square test was applied to seek association of high TLC and neutrophils count with subsequent development of heart failure. Statistical significance was taken at $p < 0.05$.

RESULT

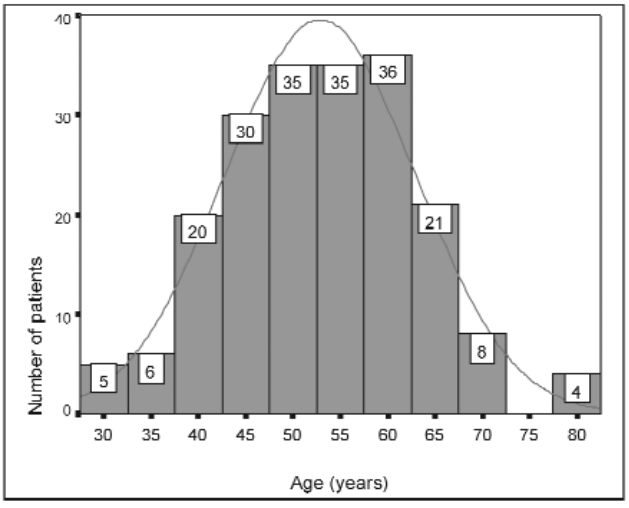
Total 200 patients were included with the mean age of 52.85 ± 10.07 (ranging from 30 to 80) years.149 (74.5%) were male patients and 51 (25.5%) females with M: F=3:1. (Fig 1) The Histogram of age distribution is presented in figure-2 Hypertension was

Figure-1: Sex Distribution:
n = 200



M: F = 3: 1

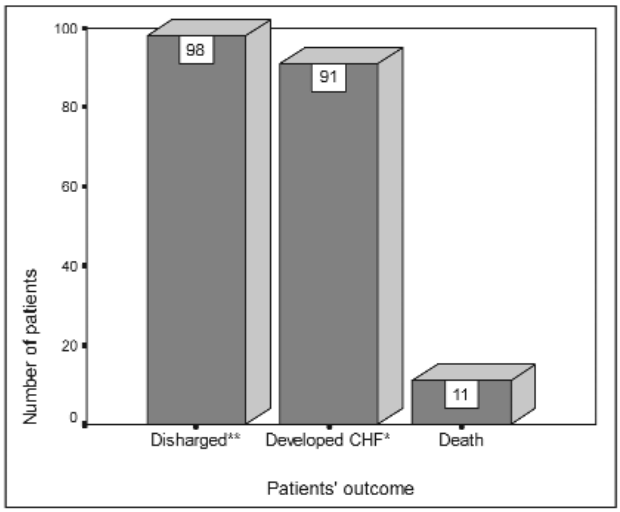
Fig-2: Age Distrubution
Mean ± SD = 52.85 ± 10.07 (Range = 30 - 80) years



the commonest risk factor that was observed in 93 (46.5%) patients followed by smoking in 92 (46%), diabetes in 83 (41.5%), family history of ischemic heart disease in 37 (18.5%), dyslipidemia in 24 (12%) and obesity in 20 (10%) patients. Anterior wall MI was the commonest diagnosis that was made in 102 (51%) patients followed by inferior wall MI in 68 (34%), posterior wall MI in 14 (7%) and lateral wall

MI in 16 (8%) patients (Table-1). Out of 200 patients 98(49%) remained uncomplicated did not show clinical evidence of CHF in the first 4-days; whereas 91(45.5%) developed CHF. 11 (5.5%) died in hospital. (Figure-3). Out of 91 patients who had clinical CHF

Figure-3: Outcome of the Patients: n = 200



** did not developed clinical CHF.
* developed CHF.

underwent echo 20(21.8%) had EF>40% and 71 (78.2%) had <40% .Majority of patients who developed CHF had anterior wall MI and 25 patients(%) who were thrombolysed developed CHF. Four patients each developed hypotension and cardiogenic shock. Out of 91 patients who developed CHF, 61 (67%) had high WBC (≥ 11000 mm^3), while 30 (33%) had normal (< 11000 mm^3) WBC. Significant association (p < 0.008) of high total leukocyte count with development of CHF was observed (Table-2). Similarly 81 (89%) had high neutrophil count (>65 mm^3),while 10 (11%) had normal (≤65 mm^3) neutrophil count. Significant association (p < 0.016) of neutrophilia with development of CHF was observed (Table -4)

Out of 11 patients who died 2 had total TLC <11,000 patients and 9 belonged to >than 11,000 (P<0.0001) and there was only 1 patient who had neutrophil count <65 mm3 and rest of 10 patients were with >65mm3 and 3 of them suffered from cardiogenic shock and 7 of them died due to arrythmia. Treatment given during the first 4-days not at time of discharge shown in Table-6. We believe % of utilization of ACE-inhibitors and beta blockers would have increased at the time of discharge as the previous statistics of this institute indicate (reference).

DISCUSSION

In support of an inflammatory cause for CHF after acute myocardial infarction, several international data confirms the relationship.[15,16,17,18]

The physiologic basis for the association between neutrophilia and the risk of Coronary events after AMI has been studied in several clinical studies that consistently demonstrated intense systemic activation of neutrophils in patients with acute coronary syndromes.[19-21] Neutrophils are the first leukocytes to infiltrate the infracted myocardium.[22-23] Activated neutrophils release a variety of proteolytic enzymes including elastase[19] and myeloperoxidase[20-21] with potential for tissue destruction.[24] The inflammatory response fosters cytokine release[25] which may promote demargination of intravascular neutrophils

Table-1: Diagnosis at the time of Presentation: n = 200

Diagnosis	Number of patients (n=200)	Percentage %
Anterior wall MI	102	51
Inferior wall MI	68	34
Posterior wall MI	14	7
Lateral wall MI	16	8

MI = Myocardial infarction

Table-2: Association of Congestive Heart Failure with High White Blood Cell in Acute Myocardial Infarction Patients: n = 200

	White blood cell (WBC)		Total	P- value
Outcome	Normal (<11000 mm³) (n=83)	High (≥11000 mm³) (n=117)		
Without clinical HF	51 (52.0)	47 (48.0)	98	
Developed CHF	30 (33.0)	61 (67.0)*	91	p < 0.008

Given values in parentheses are percentages.
CHF= Congestive heart failure
*Significant association of CHF with high WBC (>11000) at (χ^2=9.68, p<0.008).

Table-3: Association of Mortality with High White Blood Cell in Acute Myocardial Infarction Patients

	White blood cell (WBC)		Total	P-value
Outcome	Normal (<11000 mm³) (n=83)	High (≥11000 mm³) (n=117)	**(n=200)**	
Expired	2 (18.2)	9 (81.8)	11	p < 0.001

Table-4: Association of Congestive Heart Failure with Neutrophilia in Acute Myocardial Infarction Patients: n = 200

	Neutrophil count (NC)		Total	
Outcome	Normal (≤65 mm³) (n=37)	Neutrophil Count (>65 mm³) (n=163)		
Patients without clinical HF	26 (26.5)	72 (73.5)	98	
Patients with clinical CHF	10 (11.0)	81 (89.0)*	91	p< 0.016

Given values in parentheses are percentages.
CHF= Congestive heart failure
*Significant association of CHF with neutrophil count (>65) (χ^2 = 8.24)

and acceleration of the release of neutrophils by the bone marrow. In addition, there is evidence for prolongation of the lifespan of neutrophils in unstable plaques[26]

Copper et al[15] assessed that each increase in TLC of 10,000/mm³ was associated with an increased risk of death with ischemic LV dysfunction, but not for those with non-ischemic left ventricular dysfunction, in addition a baseline white blood cell count (WBC) count > 7000 was an independent predictor of all cause mortality in patients with ischemic cardiomyopathy.

Table-5: Association of Mortality with Neutrophilia in Acute Myocardial Infarction Patients

	Neutrophil count (NC)		Total	P-value
Outcome	Normal (≤65 mm³) (n=37)	Neutrophil count (>65 mm³) (n=163)	(n=200)	
Expired	1 (9.1)	10 (90.9)	11	p< 0.002

Table-6: Treatment Given:
n = 200

Treatment	Number of patients	Percentage
Clopidogrel	199	99.5
Statin	196	98
Aspirin	196	98
Strepto Kinase	142	71
Angio tensiongen converting enzyme inhibitor	175	87.5
Beta blocker	119	59.5
Low molecular weight heparin	51	25.5
Diuretic(Spiranolactone)	99	49.5
Diuretic (frusemide)	135	67.5
Inotropic support^	16	8
Conventional heparin	2	1.5
Calcium channel blocker	01	0.5

Barron et al[16] shown a higher chances of development of new congestive heart failure or shock with a higher WBC count. There is 0% chance of developing CHF if the white blood cell count ranges up to $5x10^9$/l as compared to 17.1% incidence of developing new CHF if white blood cell count were more than $15x10^9$/l. confirming a high relationship.

Christopher et al[17] documented that, the combination of death or thrombotic stroke and development of new or worsening severe congestive heart failure or cardiogenic shock was more frequent among patients with WBC count more than 10,000.

Engstrom et al[18], showed that patient with high leukocyte count at initial presentation after MI were associated with increased incidence of hospitalization due to heart failure in their long term follow-up.

All these studies confirmed that WBC represents a marker of inflammation, and the amount of inflammation may be directly related to plaque instability and LV dysfunction resulting in recurrent short and long term recurrent cardiac events.[27] A study done by Mark I. Furman showed that there is an association of WBC count with the development of heart failure and death in patients with AMI if admission TLC was > 12,000 mm the incidence of heart failure was 30.1%(p< .001) as compared to patient who had admission TLC < 6000 mm, the incidence of heart failure was 17% respectively.[28]

In our study, significant association was noted as regard to WBC with the development of CHF after

AMI ($p < 0.008$). So these results are comparable with that reported in other studies. Infact a large number of patients develop clinical CHF as compared to other studies (43% compared with the 17% to 23% that was reported in other studies)[29], supporting our hypothesis regarding association of high WBC with development of CHF. Reasons for high prevalence of clinical CHF may be due to presence of increase co-morbid in our patients or due to late arrivals and referral of sick patients to this tertiary care hospital.

Rashidi et al[30] and Lorraine Kyne et al[31] demonstrated in their study that absolute neutrophilia (>65%mm^3) during first 12 hours after acute MI predict the occurrence of HF during hospitalization. In our study, out of 91 patients who developed congestive heart failure, 81 (89%) had high neutrophil count (>65 mm^3), while 10 (11%) had normal (≤65 mm3) neutrophil count and significant association ($p < 0.016$) of neutrophilia with development of CHF was observed. The absolute peripheral neutrophil count may be a marker of the severity of myocardial inflammation due to ischemic injury or of the severity of the inflammation of the coronary arterial tree.[32] Increased neutrophil counts may also, in part, be explained by a lower probability of successful reperfusion[33-34] or impaired microvascular perfusion.[33] It is believed that the neutrophil count may represent combinations of the aforementioned potential mechanisms.

Our study has strongly shown this association so measuring /or documenting the presence of relative neutrophilia on admission to the hospital in patients with symptoms of AMI may be a useful early indicator of patients at high risk who may benefit from more aggressive interventions to prevent or reduce the risk of CHF in future.

In their study Furman et al[28] examined the association between WBC count and mortality using data from the Worcester Heart Attack Study. Consistent with the findings from the present study and the associated in hospital complications, these investigators also found that WBC count was significantly associated with in-hospital survival. Relative to those patients with the lowest WBC count, patients in the highest quantile of WBC count had 71% greater odds of dying from their AMI (OR = 1.71, 95% CI = 1.14 to 2.58). Similar study from Spain by Julio et al[35] has confirmed the relationship between WBC and hospital mortality in patient with AMI .They showed if TLC count is < 10,OOO mm, mortality was 12.7%, if TLC is between 10-14.9,000 mm mortality was 21.3%,and if TLC was >15000 mm the mortality was 35.4%. Our study also demonstrated that out of total 11 expires, [9] patient had high TLC and 10 had increased neutrophilia (p 0.001). Associated complication like cardiogenic shock,life threatening arrhythmias were also common in patients with increase neurophilia.

Our study also highlights the optimal treatment of patients with MI in tertiary care centre. As shown in table 6, almost all patients were given aspirin, clopidogrel and statins. About 88 % of patients were given ACE and 60 % were given beta blockers.

Although several other specific bio markers such as elevated pro –BNP & BNP levels would have been more sensitive and specific for diagnosing CHF, however their non availability in our set up and poor resources of patients made us to choose clinical criteria.C-reactive proteins are sensitive but not specific marker of heart failure.

LIMITATIONS

This study has several limitations; it can be generalize only to similar population in tertiary referral centers. Although in the current study those patients with conditions that may be associated with neutrophilia were excluded, it is still possible that the association between neutrophilia and CHF may be partly caused by confounding effects of other risk factors that were not controlled for in the current study. Cigarette smoking was not controlled for in this study, although previously it has been shown to be associated with leukocytosis and the risk of ischemic events.[36] In addition, there is no prior evidence that it is an independent risk factor for CHF, which was our outcome of interest in the current study. Another limitation of this study is that the neutrophil count was measured at only one point in time, and this point (although within 12 hours of symptom onset) was not consistent in all patients studied. Serial neutrophil counts, might have been more helpful in identifying high-risk individuals early. A prospective clinical study of patients with chest pain, in whom prior neutrophil counts are available, would help to address

these issues. Measurements of cytokine levels or markers of myocardial injury and neutrophil activation such as serum C-reactive protein, serum neutrophil elastase, or myeloperoxidase could also give a more accurate reflection of the myocardial inflammatory response.

IMPLICATION

We suggest that WBC is a useful biochemical tool for risk stratification of patients with AMI. In particular, we would like to draw attention to the following logistic points:

1. Determination of WBC is systematically applied in clinical protocols for AMI and current clinical practice guidelines recommend basic blood analysis in response to chest pain consistent with coronary heart disease.

2. Analysis of WBC is widely available

3. The WBC is obtained early: determination of the WBC in patients with AMI can be performed in the first few hours in any emergency department, unlike analysis of other inflammatory markers, which require reagents that are not normally available in an emergency department laboratory.

4. The cost of determining the WBC is low and, given that it is determined Systematically, does not represent an additional cost in current procedures.

CONCLUSION

The results from this study show that elevated initial high leukocyte and neutrophil count appear to be an independent predictor for the development of CHF and show trend towards increase mortality, in patients with acute STEMI.

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