# Leukocytes Count and Neutrophil/Lymphocytes Ratio in Predicting In-Hospital Outcome after Acute Myocardial Infarction

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**Abstract**

**Background:** After an acute myocardial infarction, Leukocytosis and increase neutrophils to lymphocytes ratio (NLR) may be associated with increased risk of in-hospital heart failure, and death.

**Objectives:** To evaluate the role of total WBC count and NLR as an in-hospital predictor for adverse events (death and heart failure) for the patients presented with acute MI.

**Methods:** A total of 98 patients who had no history of heart failure presented with acute myocardial infarction were studied in Marjan Teaching Hospital along their hospitalization period (i.e. for one week) by measuring total WBC count and NLR for each patient; Echocardiography and chest x-rays were done for patients to determine whom developed heart failure, any death occured during hospitalization had been also documented.

**Results:** Patients were divided into 3 groups according to a cut lines (mean & 80 centile), ($1^{st}$ centile = 48 patients, $2^{nd}$ centile = 29 patients, $3^{rd}$ centile = 19 patients).
Most patients with high baseline WBC count were associated with the development of heart failure (p value <0.05) and increase in-hospital mortality (p value <0.05).
Regarding the NLR it showed that higher ratio was associated with the development of heart failure (P value < 0.05), and with increasing mortality.
WBC count and NLR were independent predictors of in-hospital death after application of the Binary Regression Analysis.

**Conclusion:**

1- WBC count and NLR are predictors of adverse in-hospital outcome (heart failure and death) after acute myocardial infarction.
2- Both WBC count and differential ratio (NLR) are independently acting as predictors for in-hospital mortality.

## تعداد كريات الدم البيضاء ونسبة الخلايا المتعادلة إلى اللمفاوية لتنبؤ حصيلة رقاد المستشفى بعد أحتشاء العضلة القلبية

**الخلاصة**

بعد حصول أحتشاء العضلة القلبية الحاد وجد إن زيادة كريات الدم البيضاء وارتفاع نسبة الخلايا المتعادلة إلى اللمفاوية ربما يصاحبه زيادة حدوث عجز القلب ألرقادي في المستشفى وزيادة حدوث الوفاة.

**الاهداف**: لتقييم دور تعداد كريات الدم البيضاء الكلي ونسبة الخلايا المتعادلة إلى اللمفاوية في تنبؤ العواقب الوخيمة لرقاد المستشفى (عجز القلب والوفاة) للمرضى الممتثلين باحتشاء العضلة القلبية.

**الطرق**: ما مجموعه ثمان وتسعون مريضا ليس لديهم تاريخ مرضي فيما يخص عجز القلب حضروا باحتشاء العضلة القلبية الحاد كانت قد تمت دراستهم في مستشفى مرجان التعليمي وخلال طول فترة رقادهم في المستشفى (لمدة أسبوع) حيث تم احتساب تعداد كريات الدم البيضاء الكلي ونسبة الخلايا المتعادلة إلى اللمفاوية ولكل مريض؛ كذلك تم أجراء فحص صدى القلب لهم واخذ أشعة الصدر لهم لتحديد من هم قد أصيبوا بعجز القلب, كذلك أية وفاة تحصل خلال فترة الرقاد في المستشفى فانه يتم تسجيلها.

**النتائج**: لقد تمت دراسة ثمان وتسعون مريضا تم تقسيمهم إلى ثلاثة مجاميع حسب نقاط حدية (المتوسط ونسبة الثمانون بالمئة)(المجموعة العشرية = 48 مريضا , المجموعة العشرية الثانية = 29 مريضا , المجموعة العشرية الثالثة = 19 مريضا).

المرضى الذين كان لديهم تعداد كريات دم بيضاء أولي عال كانوا مصحوبين بحصول عجز القلب (نسبة الأرجحية <0,05) مع زيادة نسبة وفيات رقاد المستشفى (نسبة الأرجحية <0,05).

أما فيما يخص نسبة الخلايا المتعادلة إلى اللمفاوية فأنه قد تبين بان النسب العالية تكون مصحوبة بحصول عجز القلب (نسبة الأرجحية <0,05) ومع زيادة الوفيات (نسبة الأرجحية <0,05).

**الاستنتاج**

1. تعداد كريات الدم البيضاء ونسبة الخلايا المتعادلة إلى اللمفاوية تعتبر عوامل تنبؤية للحصيلة الوخيمة لرقاد المستشفى (عجز القلب والوفاة) بعد احتشاء العضلة القلبية الحاد.
2. إن تعداد كريات الدم البيضاء ونسبة الخلايا المتعادلة إلى اللمفاوية كلاهما يعمل بصورة مستقلة كعامل تنبؤي لحصول وفيات رقاد المستشفى.

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## Introduction

Acute myocardial infarction (AMI) is one of the most common diagnoses in hospitalized patients in industrialized countries.

Leukocytes are the major cellular counterparts of inflammation and immune response; they include neutrophils, lymphocytes, monocytes, basophils and eosinophils.

They have been assigned specific functions, such as destruction of bacteria by neutrophils in many disease processes, and many of the functions of the WBC types have been studied and nearly understood completely. [1]

Elevation of the total leukocyte count is probably caused by the increase in cortisol levels during an acute stress reaction. [2]

The white blood cell (WBC) count has been established as a marker of inflammation, [3]

In coronary artery disease (CAD) inflammation plays a key role at all stages; [4,5] in the initiation and progression of cardiovascular disease.[6,7]

Different inflammatory biomarkers, such as C-reactive protein and leukocyte counts, are used in clinical practice for cardiac risk stratification in stable CAD as well as in acute coronary syndromes. [8,9]

Elevated white blood cell play important role in the vascular injury and atherogenesis, the development of an atherosclerotic plaque rupture, and thrombosis. [10-12]

White blood cell (WBC) count and its subtypes have been studied as inflammatory biomarkers to predict cardiovascular outcomes in patients with and without coronary artery disease. [13]

Aims of this study are:

1. To evaluate the role of total WBC count as a predictor of in-hospital prognostic factor (death and heart failure) for the patients presented with acute MI.
2. To evaluate the role of differential WBC count ratio (NLR) as an in-hospital predictor for adverse events (death and heart failure) for the patients presented with acute MI.

## Patients and Method

The study included 98 patients admitted to the coronary care unit of Marjan teaching hospital diagnosed as acute myocardial infarction from the period of 15/12/2008 till 20/5/2009.

The criteria for enrollment are elevation of the CK-MB (creatine kinase – myocardial band) above the $99^{th}$ centile (a value of CK-MB $\geq$ 25U/l was considered positive) in patient presented with typical ischemic chest pain with electrocardiographic evidence of ST segment elevation.

Two venous blood samples were taken, at the time of inserting the i.v line i.e. before any medical intervention (the first hour of admission).

The first blood sample for WBC count and differential (NLR) collected with EDTA tube (2mg/dl EDTA anticoagulant) and the second sample for cardiac enzymes CK-MB using plane tube.

WBC count and differential study was determined by two expert hematologists. Differential WBC counts include neutrophils, lymphocytes and monocytes. The NLR counted deploying the absolute count method.

A quantitative assessment of the CK-MB level using Randox CK-MB Kit (Cat. No. CQ 3100) and the method deploying spectrophotometric procedure using spectrophotometer Cecil 1011 French 2000 and the centrifuge is Centrifuge Hettich Rotofix 32A Germany 2005.

Patients discharged before day 6 from the admission were excluded from the study, 2 cases were excluded due to premature discharge to home.

A full history was taken concentrating on risk factors including gender, diabetes, hypertension, smoking, family history of premature coronary heart disease and sudden cardiac death of unknown cause.

Physical examination was done including assessment of blood pressure, pulse rate, and temperature searching for exclusion criteria like infection.

Patients with history of hematological disease, infection, recent trauma or surgery, using of any medications that can affect WBC count or differential count (example: steroids, cytotoxic medications … etc.), history of renal failure, history of connective tissue disease and history of heart failure were excluded from the study.

Diabetes was determined by referral physician report and was based on a fasting blood sugar level $\geq$ 126 mg/dl or use of antidiabetic medications [1].

Hypertension was determined by a value of systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90mmHg or the use of antihypertensive medications.

Smoking included active smoking or $\geq$ 10 packs/year tobaccos uses [1].

positive Family History include first degree relatives with history of premature coronary heart disease ( males < 55 years old and females < 65 years old ) which includes history of angina, myocardial infarction, sudden cardiac death of unknown cause [1].

Heart failure was diagnosed depending on clinical assessment, chest x-ray, and echocardiography using Echo Philips USA EnVisor C series 98041 – 3003.

Patients were followed daily for 7 days in the hospital looking for the clinical

development of heart failure aided by CXR and echocardiography. Also any event of death was recorded for the cases involved by the study.

**Statistical Analysis**

Data were expressed as means ± standard deviation (SD).Chi-square test was used to test the relationship between different parameters. A *P* value of 0.05 or less was considered to be statistically significant.

Statistical comparisons were performed using PASW Statistics (ver.18 polar engineering and consulting .USA). Because some cells have values to be expected less than 5; The Fisher's exact test was used to calculate the results.

Patients were divided into 3 groups according to a cut lines (mean & 80 centile) and grouped according to that into three centiles ($1^{st}$ centile = 48 patients, $2^{nd}$ centile = 29 patients, $3^{rd}$ centile = 19 patients).

If the measured parameters were not normally distributed, Skewness has been measured and If the distribution of each variable was markedly skewed (i.e. had a skewness coefficient exceeding 1.00), a natural logarithmic transformation was applied. Correlations between variables were analyzed deploying a binary regression analysis.

Diabetes and hypertension were used as independent variables, first testing each one separately, and then adding them to the multivariate model. In order to evaluate the independent prediction ability of WBC count and NLR on the outcome.

**Results**

On the bases of data from 96 patients, there were 72 males and 24 females (M: F ratio =3:1), of age ranged 29-75 year (mean 52 years ± 7.1 SD) of whom there were 18 diabetics (18.7%) , 33 hypertensive (34.4%) and 56 smokers (58.3%). The patients were divided into 3 groups according to the WBC count tertiles and NLR tertiles as the following:-

Regarding the WBC count the tertiles were the following:-

$1^{st}$ tertile: - 3000-8399 cells/$mm^3$

$2^{nd}$ tertile: - 8400-12499 cells/$mm^3$

$3^{rd}$ tertile: - 12500-20000 cells/$mm^3$

Regarding the NLR the tertiles were the following:-

$1^{st}$ tertile: 1 - 1.999

$2^{nd}$ tertile: 2 - 3.649

$3^{rd}$ tertile: 3.65 - 6.2

The baseline characteristics across the patients in the study by their admission WBC count tertiles are shown below:-

**Table 1** Base line characteristics according to WBC tertiles

| | | WBC tertiles | | | Total |
|---|---|---|---|---|---|
| | | 1st tertile | 2nd tertile | 3rd tertile | |
| No. of Patients | | 48 (50%) | 29 (30.2%) | 19 (19.8%) | 96 (100%) |
| Age (years ) | | 29-71 Mean 57.97 ± 8.84 SD | 45-70 Mean 58.38 ± 7.37 SD | 29-75 Mean 62.05 ± 11.84 SD | |
| Sex | Male | 34 (70.8%) | 24 (82.8%) | 14 (73.7%) | 72 (76%) |
| | female | 14 (29.2%) | 5 (17.2%) | 5 (26.3%) | 24 (24%) |
| Diabetics | | 13 (27.1%) | 1 (3.4%) | 4 (21%) | 18 (18.7%) |
| Hypertensive's | | 24 (50%) | 5 (17.2%) | 4 (21%) | 33 (34%) |
| Smoking | | 48 (100%) | 5 (17.2%) | 3 (15.8%) | 56 (58.3%) |

The baseline characteristics across the patients in the study by their admission NLR tertiles are shown below:-

**Table II** Base line characteristics according to NLR tertiles

| | | NLR tertiles | | | Total |
|---|---|---|---|---|---|
| | | 1st tertile | 2nd tertile | 3rd tertile | |
| No. of Patients | | 48 (50%) | 29 (30.2%) | 19 (19.8%) | 96 (100%) |
| Age ( years ) | | 29-72 Mean 55.71 ± 9.44 SD | 39-70 Mean 60.17 ± 8.59 SD | 59-75 Mean 65.05 ± 4.98 SD | |
| Sex | Male | 39 (81.2%) | 22 (75.8%) | 11 (58%) | 72 (76%) |
| | female | 9 (18.8%) | 7 (24.2%) | 8 (42%) | 24 (24%) |
| Diabetics | | 1 (2%) | 9 (31%) | 8 (42%) | 18 (18.7%) |
| Hypertensive's | | 14 (29.2%) | 11 (37.9%) | 8 (42%) | 33 (34%) |
| Smoking | | 27 (60.4%) | 18 (62.1%) | 11 (58%) | 56 (58.3%) |

This study showed that the incidence of heart failure increased with the increment of the WBC count (it was more in the 3rd tertile)as shown in the following table.

**Table III** shows the relationship between WBC tertiles and incidence of heart failure among patients in the study.

| WBC tertiles | Heart Failure | No Heart Failure | Total |
|---|---|---|---|
| 1st tertile | 1 (2%) | 47 (98%) | 48 |
| 2nd tertile | 3 (10.2%) | 26 (89.8%) | 29 |
| 3rd tertile | 4 (21%) | 15 (79%) | 19 |
| Total | 8 (8.3%) | 88 (91.7%) | 96 |

P value < 0.05

This study showed that the mortality was higher in the patients with higher WBC count (3rd tertile)as shown in the following table.

**Table IV** shows the relationship between WBC tertiles and incidence of mortality among patients in the study.

| WBC tertiles | Death | Survival | Total |
|---|---|---|---|
| 1st tertile | 1 (2%) | 47 (98%) | 48 |
| 2nd tertile | 2 (6.9%) | 27 (93.1%) | 29 |
| 3rd tertile | 4 (21%) | 15 (79%) | 19 |
| Total | 7 (7.3%) | 89 (92.7%) | 96 |

P value < 0.05

This study showed that the incidence of heart failure increased with the increment of the NLR (it was more in the 3rd tertile)as shown in the following table.

**Table V** shows the relationship between NLR tertiles and incidence of heart failure among patients in the study.

| NLR tertiles | Heart Failure | No Heart Failure | Total |
|---|---|---|---|
| 1st tertile | 1 (2%) | 47 (98%) | 48 |
| 2nd tertile | 2 (6.9%) | 27 (93.1%) | 29 |
| 3rd tertile | 5 (26.3%) | 14 (73.7%) | 19 |
| Total | 8 (8.3%) | 87 (91.7%) | 96 |

P value < 0.05

This study showed that the mortality was higher in the patients with higher ratio (3rd tertile)as shown in the following table.

**Table VI** shows the relationship between NLR tertiles and incidence of mortality among patients in the study.

| NLR tertiles | Death | Survival | Total |
|---|---|---|---|
| 1st tertile | 0 (0%) | 48 (100%) | 48 |
| 2nd tertile | 2 (6.9%) | 27 (93.1%) | 29 |
| 3rd tertile | 5 (26.3%) | 14 (73.7%) | 19 |
| Total | 7 (7.3%) | 89 (92.7%) | 96 |

P value < 0.05

The association with heart failure and death was independent to diabetes and hypertension after application of the Binary Regression Analysis for both

the NLR and WBC count. (Table VII and Table VIII).

**Table VII** WBC groups independency for mortality after application of the binary regression logistic analysis using LR method.

| Variable | Significance |
|---|---|
| Diabetes Mellitus | 0.02 |
| Hypertension | 0.02 |
| WBC Groups | 0.008 |

**Table VIII** NLR groups independency for mortality after application of the binary regression logistic analysis using likelihood ratio method.

| Variable | Significance |
|---|---|
| Diabetes Mellitus | 0.05 |
| Hypertension | 0.03 |
| NLR Groups | 0.01 |

## Discussion

In present study, baseline total WBC count and NLR were studied among 96 patients with Acute MI; it was observed that there was a strong relationship between baseline findings of relatively simple, inexpensive predictors of poorer in-hospital outcome for this patient's group .

Earlier studies have shown WBC count to be an independent predictor of short-term mortality in patients with acute myocardial infarction. Different leukocyte subtypes vary in their prognostic implications in patients with acute myocardial infarction. Elevated neutrophils have shown to be associated with worse angiographic outcomes, large infarct size, and poor short-term prognosis in ST-segment elevation myocardial infarction. Neutrophils mediate the inflammatory response to acute myocardial injury by numerous biochemical mechanisms, resulting in further tissue damage. They include the release of arachidonic acid metabolites and platelet-aggravating factors, cytotoxic oxygen–derived free radicals, myeloperoxidase, elastase, various hydrolytic enzymes such as acid phosphatases, and so on. [14]

This study showed that elevated WBC count was adversely associated with poorer outcome regarding the cardiac function with subsequent development of heart failure within the first week of the event of myocardial infarction which was statistically significant (p value <0.05) and it is higher in the 3$^{rd}$ tertile (21%) while other tertiles 1$^{st}$ tertile=2%, 2$^{nd}$ tertile=10.2%, This agrees with studies Vandana Menon et al [15] (1$^{st}$ tertile=14.3%, 5$^{th}$ tertile =24.8%) (P value<0.001), Mark I. Furman et al study [16] (1$^{st}$ tertile=7.2%, 4$^{th}$ tertile=12%) (P

value<0.001), Christopher P. Cannon et al study [17] (1st tertile =1.3%, 4th tertile=3.6%) (P value <0.001). There was strong evidence that elevated WBC counts during ACS especially myocardial infarction is associated with increased risk of mortality, heart failure, shock, and left ventricular dysfunction. Leukocytes may directly mediate adverse outcomes through their biochemical properties or may indirectly measure inflammatory and/or thrombogenic states [17].

This study showed that patients with high baseline WBC count were associated with increase in-hospital mortality (during the first week) which was statistically significant (p value <0.05) and it was higher in the 3rd tertile (21%) while other tertiles 1st tertile=2%, 2nd tertile=6.9%, This was in agreement with the three largest studies that performed by Grzybowski et al [10] (1st tertile=7.1%, 5th tertile=15.9%) (P value< 0.001), and study by Barron et al [18] (p value< 0.001) and it was also higher in the 3rd tertile(1st tertile=1.4%, 3rd tertile= 3.3%) and another study by Christopher P. Cannon et al [17] also showed the same (1st tertile=1.4%, 4th tertile=3.3%) (P value<0.001).

Many years ago Schlant et al observed that an elevated WBC count was a predictor of mortality post MI. More recently, they have demonstrated that in the setting of STEMI, an elevated WBC count was associated with reduced epicardial and myocardial perfusion and worse clinical outcomes (both short term and long term) .

The study also showed that the association was independent of history of diabetes and hypertension, with increasing mortality with the progressive increment in the WBC count; this is in agreement with Grzybowski et al [10] and Barron et al [19] studies. It means that WBC count was independent strong predictor of in-hospital mortality in patients with acute myocardial infarction.

Regarding the NLR it was found that the association between the NLR and heart failure was also significantly associated with increasing NLR (P value <0.05) and it was higher in the 3rd tertile (1st tertile= 2%, 2nd tertile=6.9%, 3rd tertile=26.3%) we find no study to prove or refute that.

The study also showed that mortality was significantly associated with increasing NLR which appeared at higher level at the third tertile (26.3%) other tertiles 1st tertile=0%, 2nd tertile=6.9 %(p value < 0.05). This is in agreement with the study by Umesh U. Tamhane et al [14] their study showed that patients in the 3rd tertile had the highest in-hospital mortality (8.5%) as compared to the 1st and 2nd tertiles in their study (1.8% & 3.4%) respectively (p value<0.001) another study done by Radhi H.Hassan showed same pattern of increasing mortality (1st tertile= 0%, 2nd tertile= 25%, 3rd tertile= 75%) (P value <0.05).

This study also showed that NLR was independently for DM and hypertension in association with death this is in agreement with the study done by Umesh U. Tamhane et al [14].

The study also showed that even in patients with normal WBCs count there was increasing risk of death if the NLR is high for the patient (as this observation occured in two patients).

## Conclusion

1. WBC count is an important, relatively inexpensive and widely available strong predictor of adverse in-hospital outcome and can be applied as a routine test in our hospitals.
2. NLR (relative neutrophilia in association with lymphopenia) in patients with normal WBCs count is important and strong predictor of adverse in-hospital outcome for patients presented with acute MI (heart Failure and death)

3. Both WBC count and differential ratio (NLR) are independently acting as predictors for adverse outcome in predicting death, even after adjusting other associated important risk factors (DM and Hypertension).

**Recommendations**

1. WBC count and differential could be used to guide our management for patients with acute MI having the highest ratio and count to put them under aggressive strategies of treatment aiming to prevent adverse in-hospital outcome.
2. Further studies are needed which is better to be extended in number of cases and in spectrum to involve wide patients' group (all patients with acute coronary syndrome)
3. Further studies are needed to prove our finding for the association between the elevated NLR and the subsequent development of heart failure in the short term.

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