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Original Article

Association of Neutrophil to Lymphocyte Ratio with In- hospital Outcome of Acute Heart Failure due to Acute Anterior ST-elevation Myocardial Infarction

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Key Words : *Acute heart failure, Mortality, Outcome, Neutrophil-to-lymphocyte ratio.*

Abstract:

Background: *Early detection and appropriate management play a key role in reducing the morbidity and mortality of acute heart failure in patients with acute myocardial infarction. Many prognostic factors have been assessed till date. This study aimed to evaluate the prognostic effect of NLR on in-hospital outcomes in patients with acute heart failure due to acute anterior ST elevation myocardial infarction.*

Methods: *The present study was carried out in the Department of cardiology, Sir Salimullah Medical College & Mitford Hospital, Dhaka from January 2020 to December 2020. A total of 88 cases of acute heart failure due to acute anterior ST elevation Myocardial infarction patients are enrolled in this study. NLR was estimated and patients were divided into two groups based on the NLR (Group I NLR <6; Group II NLR ≥6). Then in-hospital outcome was observed and compared between two groups.*

Results: *In-hospital mortality and length of hospital stay were higher among NLR ≥6 patients with statistical significance (11.6% vs. 40.9%, p<0.001). These patients also had high incidence of cardiogenic shock (25% vs. 43%, p>0.072), Arrhythmia (18% vs. 34%, p>0.089) but without statistically significant difference.*

Conclusion: *In this study, we observed that in-hospital outcomes were worse in patients with acute heart failure due to acute anterior myocardial infarction with NLR ≥6. So NLR can be used as a predictor of outcome in acute heart failure patients. This association is independent of conventional cardiovascular risk factors.*

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Introduction:

Acute heart failure (AHF) carries a major health burden, with significant morbidity and mortality. In the majority of cases acute heart failure can be attributed to worsening chronic heart failure. Approximately 60% of patients with AHF have documented coronary artery disease. Among them, acute myocardial infarction (segmental dysfunction) specially acute anterior ST elevation myocardial infarction is a major cause of heart failure. The possible mechanism is reduced ventricular contractility.[1]

The prevalence of heart failure is approximately 1 to 2% in developed countries, rising to >10% among people over 70 years of age. The lifetime risk of heart failure at age 55 years is 33% for man and 28% for woman.[2] Despite treatment advancements, 50% of patients die within 5 years

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of diagnosis.[3] HF may be associated with a wide spectrum of LV functional abnormalities, which may range from patients with normal LV size and preserved ejection fraction (EF) to those with severe dilatation and/or markedly reduced EF. In most patients, abnormalities of systolic and diastolic dysfunction coexist, irrespective of EF.[4,5]

Incidence of heart failure among patients hospitalized for an acute myocardial infarction ranges from 14 to 36%. Despite therapeutic advances, the prognosis of acute heart failure is poor, with in- hospital mortality ranging from 4 to 7%. The mean duration of hospitalization was 4 to 7 days. After adjudication, 79.6% died due to cardiac problems; among them 62.2% due to pump failure, 3.7% due to sudden cardiac death and 34.1% due to acute coronary syndrome or acute myocardial infarction.[6] Acute heart failure can be risk stratified by Killip classification (clinically) after acute myocardial infarction and also by NT-Pro BNP and Echocardiography. Neutrophil to Lymphocyte Ratio (NLR) is used as a new additional inflammatory marker to see the prognosis of acute heart failure patients.[7]

The application of a simple blood test to predict prognosis in acute heart failure patients is not well established. NLR is inexpensive and easy to obtain in hospitalized patients using a routine blood test. In AHF patients, higher NLR increases in-hospital mortality and morbidity.[8]

Two possible mechanisms are suggested why higher NLR predict the poor outcome in patients with HF. First, NLR is an inflammatory marker. Second, NLR reflects sympathetic tone. NLR is a combination of two independent inflammatory markers involved in two different immune pathways: neutrophils as a marker of the ongoing nonspecific inflammation are involved with a much quicker response, and lymphocytes as a marker of the regulatory pathway are associated with more adaptive long-term response of the immune system.[9] Another plausible mechanism is that NLR can be affected by autonomic nerve balance. In other words, a higher NLR could imply a higher ratio of sympathetic/parasympathetic tone.[10] High NLR is associated with myocardial dysfunction.[11] No study was done previously in Bangladesh in relation of NLR with AHF due to acute anterior myocardial infarction. Aim of this study is to evaluate the Association of NLR with in-hospital outcome of AHF due to acute anterior STEMI.

Methods:

This present study was designed as cohort study at Department of Cardiology, Sir Salimullah Medical College & Mitford Hospital, Dhaka. This study was conducted from January, 2020 to December, 2020. Eighty eight patients admitted in the Department of Cardiology with acute heart failure or developed heart failure after admission due to acute anterior ST elevation myocardial infarction were included in the study. The samples were collected by convenient sampling method. Study population was divided into two groups on the basis of NLR. In Group I, NLR < 6 (low-risk group) and group II, NLR ≥6 (high-risk group). Then routine follow-up and close monitoring of the admitted patients. Patients with hematological disease, neoplastic metastases to the bone marrow, sepsis, severe anaemia, pregnancy, severe arthritis, inflammatory bowel diseases, infection, chronic inflammatory conditions, glucocorticoid therapy, a history of glucocorticoid use 3 months before admission, other extracellular fluid-increasing diseases (e.g., hypothyroidism and cirrhosis of liver) were excluded from this study.

Informed written consent was taken from each patient before enrollment. Meticulous history was taken and detailed clinical examination was performed. In brief, patients who had signs or symptoms of AHF such as either dyspnoea, orthopnoea, cough, chest heaviness, pulmonary edema were enrolled in the study. Necessary physical examinations were done including pulse, blood pressure, jugular venous pressure, basal crepitation, auscultation for any cardiac murmur. Risk factors profile including smoking, hypertension, dyslipidemia and family history of myocardial infarction were noted. All routine hematological & biochemical tests were performed after admission or within 12 hours of development of symptom. LVEF assessment was done within 24 hours of admission by using PHILIPS Affiniti 70C machine (transthoracic echocardiography). Quantitative calculation using the modified Simpson's biplane method was done. Heart failure with preserved ejection fraction (HFpEF) defined as LVEF ≥50% and heart failure with reduced ejection fraction (HFrEF) was defined as LVEF <

40%. Patients with LVEF between 40 and 49% considered to have heart failure with midrange ejection fraction (HFmrEF). All venous blood samples were obtained upon patient presentation, before administration of drugs. Total white blood cell, neutrophil, and lymphocyte counts were obtained by using an automated blood cell counter. The NLR was calculated as the ratio of the neutrophil count to the lymphocyte count. During hospitalized period, information about clinical outcomes, laboratory data were evaluated. All study protocol was reviewed and approved by the ethical Review Board of hospital. The data obtained from the study were analyzed and significance of differences were estimated by using statistical methods. Continuous variables were expressed as mean values ± standard deviation and compared using Student's t-test. Categorical variables were expressed as frequencies with corresponding percentages and compared using Chi-square test. Predictors for adverse in-hospital outcome were determined by logistic regression analysis. A p value of < 0.05 was considered statistically significant. Statistical analyses were carried out by using SPSS (Statistical Package for the Social Sciences by SPSS Inc., Chicago, IL, USA, 2015) Version 22.

Results:

The objective of the study was to find out the relation of NLR on in- hospital outcome of patients with acute heart failure due to acute anterior STEMI. Patients was divided into two groups accordingly to NLR cut-off value. 44 patients were comprised of NLR < 6 and group II, NLR ≥6.

Table-I

Distribution of study population by age (n=88).

Age (years)	Group I (n=44) No (%)	Group II (n=44) No (%)	p value
d"41	1 (2.3)	2 (4.5)	
41-50	9 (20.5)	12 (27.3)	
51-60	14 (31.8)	14 (31.8)	.751^{ns}
>60	20 (45.5)	16 (36.4)	
Mean ± SD	57.56±8.03 (SD)	56.38±8.76 (SD)	.487^{ns}
Total	44 (100)	44 (100)	

Chi-square test and Unpaired student t test to compare between two groups

Majority of the study population were > 60 years in both groups (45.5% in group I and 36.4% in group II). Age distribution was statistically similar in both groups.

Table-II

Distribution of risk factors in study population (n=88)

Risk factors	Group I (n=44) No (%)	Group II (n=44) No (%)	p value
Hypertension	26 (59.1)	28 (63.6)	.661^{ns}
Diabetes Mellitus	14 (31.8)	18 (40.90)	.224^{ns}
Dyslipidemia	21 (47.73)	23 (52.28)	.641^{ns}
Smoking	18 (40.90)	15 (17.04)	.821^{ns}
Family history of CAD (Coronary Artery Disease)	6 (13.6)	13 (29.5)	.078^{ns}
BMI ≥25	31 (70.45)	35 (79.54)	.091^{ns}

Chi square test was performed to compare between two groups

Risk factors of the study population are tabulated in table II. The most common risk factors were hypertension (61.4%) and dyslipidemia (50%) in both groups. Risk factors were statistically similar in both groups (p>.05).

Table-III

Clinical features among study population (n=88).

Clinical Features	Group I (n=44) No (%)	Group II (n=44) No (%)	p value
Symptoms			
Shortness of breath	26 (59.1)	32 (72.73)	.423^{ns}
Sweating	44 (100)	44 (100)	1.0^{ns}
Nausea	26 (59.1)	26 (59.1)	1.0^{ns}
Vomiting	12 (27.3)	16 (36.4)	.328^{ns}
Signs			
Tachycardia	27 (61.37)	29 (65.90)	.632^{ns}
High BP	21 (47.7)	19 (43.2)	.669^{ns}
Raised RR	25 (56.8)	29 (65.9)	.381^{ns}
Basal crepitation	15 (34.1)	18 (40.9)	.509^{ns}

Chi square test was performed to compare between two groups

Clinical features of study population are tabulated above. Presenting symptoms were shortness of breath (65.90%), sweating (100%), nausea (60%), vomiting (31.81%). Presenting signs were tachycardia (63.64%), high BP (45.5%), raised RR (61.4%) and basal crepitation (37.5%). Both groups were statistically similar regards to clinical presentation.

Table-IV

Laboratory findings of study population (n=88).

Investigation findings	Group I(n=44) Mean ± SD	Group II(n=44) Mean ± SD	p value
LVEF (%)	48.88±11.12	41.53±5.34	.044[s]
Troponin I (ng/ml)	13.92±9.94	14.58±7.98	.848[ns]
NT-pro BNP	2358.21±641.94	3671.67±241.24	.023[s]
S. creatinine (mg/dl)	1.06±.163	1.02±.168	.318[ns]
Random blood sugar(mmol/L)	8.28±3.45	7.66±2.80	.352[ns]
Total cholesterol(mg/dl)	261.16±52.66	246.68±52.81	.201[ns]
Triglyceride(mg/dl)	187.80±99	184.36±113.60	.880[ns]
HDL (mg/dl)	34.61±6.60	35.66±5.97	.346[ns]
LDL (mg/dl)	119.27±43.02	104.48±33.64	.076[ns]

Unpaired student t test was performed to compare between two groups

Laboratory findings of study population are tabulated above. Mean LVEF were statistically higher in patients of group I and NT-Pro BNP were statistically higher in patients of group II. Mean troponin I, s. creatinine, random blood sugar, total cholesterol, triglyceride, HDL and LDL are statistically similar in both groups.

Hematological profile of the patients are tabulated above. Mean WBC, neutrophil and NLR were significantly higher in patients with group II (p<05). Mean lymphocyte was significantly higher in group I patients (p<.05).

In this study in hospital mortality was higher among the patients with NLR > 6 with statistical significance. In group I, 43.18% patients recovered without complications while and 11.6% patients died during hospital stay. In group II, 15.9% patients recovered without complications while 40.9% patients died.

Univariate regression analysis of various predictors for in hospital mortality was done. Increasing age [OR 1.069, 95% CI (1.473-2.424), p=.038], Patients having hypertension [OR 2.385, 95% CI (1.028 – 5.537), p=0.043], dyslipidemia [OR 3.676, 95% CI (1.034 – 13.072), p=0.044] and NLR [OR 6.628, 95% CI (2.346 – 18.725), p<0.001] had significantly higher odds for in hospital mortality (p<0.05).

Table-V

Hematological investigation findings of study population (n=88).

Hematological findings	Group I (n=44)	Group II (n=44)	p value
Hb (gm/dl)Mean ± SD	10.01±2.31	10.15±2.13	.771[ns]
WBC (103cmm)Mean ± SD	8754.09±5099.84	10973.1818±4272.19	.030[s]
Neutrophil (%)Mean ± SD	63.07±15.92	71.92±19.71	.023[s]
Lymphocyte (%)Mean ± SD	22.66±11.79	8.97±3.60	<.001[s]
NLRMean ± SD	3.06±1.62	11.42±7.02	<.001[s]

Unpaired student t test was performed to compare between two groups

Table-VI

In hospital outcome of the study population (n=88).

Outcome@	Group In (%)	Group IIn (%)	p value
Recovered without complications	19 (43.18)	7 (15.9)	.005[s]
Cardiogenic shock	11 (25)	19 (43.19)	.072[ns]
Arrythmia	8 (18.19)	15 (34.09)	.089[ns]
In hospital mortality	5 (11.6)	18 (40.9)	.001[s]
Hospital stay (mean ± SD)	8.42±.55	10.57±.55	<.001[ns]

@Multiple response considered

Chi square test and independent student t test was performed to compare between two groups

Table-VII

Univariate analysis of predictors for worse outcome (in-hospital mortality) (n=88).

Variables	Odds ratio	95% CI	P value
Age	1.069	1.472 – 2.424	0.038[s]
Sex (Female)	1.063	0.446 – 2.530	0.891[ns]
Hypertension	2.385	1.028 – 5.537	0.043[s]
Smoking	1.063	0.385 – 2.936	0.906[ns]
Diabetes	1.476	0.573 – 3.803	0.420[ns]
Dyslipidemia	3.676	1.034 – 13.072	0.044[s]
NLR (>6)	6.628	2.346 – 18.725	<0.001[s]

Table-VIII

Multivariate analysis of predictors for worse outcome (in- hospital mortality) (n=88).

Variables	Odds ratio	95% CI	p-value
NLR (>6)	6.033	2.004 – 18.165	0.001s

Multivariate regression analysis of different predictors of in hospital mortality was done. NLR had OR of 6.003 (95%CI 2.004 – 18.165; p<0.001) for in hospital mortality.

Discussion:

The current study was designed to evaluate the prognostic effect of NLR with in- hospital outcome of acute heart failure due to acute anterior STEMI. After admission or within 12 hours of development of symptoms patient was divided into two groups- group I and group II. Group I included patients with NLR < 6 and group II included patients with NLR ≥6.

In this study the mean age of patients with acute anterior ST Elevation MI was 56.97±7.92 (SD) years. Age plays a vital role in the deterioration of cardiovascular functionality, resulting in an increased risk of cardiovascular disease (CVD) in older adults.[12] Similar study on the patients with STEMI were found mean age 53.75±11.64 (SD) and 57.07±12.40 years.[13,14] Incidence of CVD tends to increase with age, along with the increasing incidences of atherosclerosis, stroke and, myocardial infarction.[15]

Male predominance was observed in present study with 63.60% in group I and 77.30% in group II. Male predominance among the patients with STEMI with 72.83% male patients.[16] Female gender is considered to have lesser odds for cardiovascular disease due to positive effect of endogenous oestrogens, and relatively lower cholesterol level, especially in their premenopausal life.[17,18] Moreover, in Bangladesh, female patients are getting less priority in society. So, the frequency hospital admitted MI patients could be gender biased. Both gender and age were statistically similar in both groups. The most common risk factor was smoking, hypertension, diabetes. Hypertension, diabetes and smoking as dominant risk factors.[14] Hypertension, diabetes, smoking, dyslipidemia and family history of CAD as risk factors of STEMI.[19] All these statements are nearly concordant to the findings of present study.

Presenting clinical features of the patients were sweating, nausea/vomiting, tachycardia, high BP, raised respiratory rate and basal crepitation. No significant difference was noticed between group I and II patients regarding clinical presentations. Mean troponin I was 13.92±9.94 ng/ml in group I and 14.58±7.98 (SD) ng/ml in group II. Mean left ventricular ejection fraction was 48.88 ±11.12 and 41.53 ±5.34 in group I and group II. Mean WBC and mean neutrophil were significantly higher in group II patients. Mean lymphocyte was significantly lower in group II patients.

The NLR is a composite of two distinct inflammatory markers where increased neutrophil is an indicator of continuing nonspecific inflammation and decreased lymphocyte is an indicator of adaptive long-term immune response.[8] In this study, mean NLR was 3.06±1.62 (SD) in group I patients and 11.42±7.02 (SD) in group II patients. Overall mean NLR of the study population was 7.24±6.58. Mean NLR 7.93±6.38 among patients with STEMI which corroborate with present study.[20] The NLR has been shown to

be an indicator of death in patients with acute coronary syndrome, where a high NLR is demonstrated to be associated to a high mortality rate.[21] Present study also observed higher frequency of in hospital mortality among the patients with high NLR. In patients who had NLR e"6, 40.9% patients were died and in patients who had NLR < 6, 11.6% patients died. Positive correlation between NLR and myocardial damage and negative correlation between NLR and myocardial function.[11] A similar study observed that higher in-hospital mortality in patients with greater NLR.[8] In present study, both univariate and multivariate logistic regression showed that NLR was a significant predictor for in-hospital mortality in the study population.

The NLR is easily calculated from the differential WBC count, which is routinely performed on hospital admission and requires no additional cost, making the NLR a favorable marker compared with many other inflammatory markers. The worse outcomes of acute anterior ST elevation MI patients with a high NLR may result from their increased inflammatory activity and aggravated prothrombotic status, although the precise underlying biological mechanisms are not yet clear. Despite their short half lives, neutrophils are capable of secreting large quantities of inflammatory mediators, and neutrophilia is associated with acute inflammatory responses to tissue injury. Acute lymphopenia, especially low CD4+ T cells, is associated with poorer prognosis after STEMI. Regulatory CD4+ T cell responses are reduced by high levels of oxidized low density lipoprotein and cortisol. Consequently, a high NLR is a reflection of two opposing immune pathways and is a better predictive marker than either parameter alone. Increased circulating levels of inflammatory markers have been observed in patients with AMI, suggesting that inflammatory activation may be linked to the pathogenesis of MI. More inflammation causes more myocardial damage and less myocardial activity. So, aggravation of heart failure. Consistent with this theory, we also observed a positive association between the high NLR and in hospital mortality. Here, inflammation plays the key role and numerous inflammatory biomarkers are correlated with disease severity and prognosis across throughout heart failure. White blood cell count and its subtypes are classical markers of inflammation in cardiovascular disease and Leukocytosis increases incidence of HF hospitalization and mortality. Moreover, neutrophilia is associated with increased incidence of acute decompensated heart failure in patients with acute myocardial infarction, and lymphopenia is related to poor prognosis in patients with HF. Neutrophil-lymphocyte ratio (NLR), which neutrophils counts are divided by lymphocyte counts, is used as a new additional inflammatory marker. And present study observed that elevated NLR could be an independent predictor of outcome of heart failure.

Conclusion:

NLR is a cost-effectiveness, easy to apply value that predicts and stratifies the risk of patients with AHF. Elevated NLR in patients with AHF on admission is an independent prediction for in-hospital outcome. In this study AHF due to acute anterior STEMI who has high NLR had high hospital stay, mortality and complications. So, NLR can be used as a prognostic marker. Those who has high NLR aggressive RX was needed. Further extensive study is needed.

Limitations:

While caring out the study utmost care was taken. However, there are some important limitations. All samples were collected from a single center. Only acute anterior ST elevation MI was considered. All patients are treated with thrombolytic therapy, no primary or rescue PCI was done.

Conflict of Interest - None.

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