The Association between Neutrophil to Lymphocyte Ratio and Systolic Right Ventricular Dysfunction in Patients with Acute Inferior ST- Segment Elevation Myocardial Infarction

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Abstract

Background: Ischemic heart disease is considered the most common cause of death worldwide. Inflammation and oxidative stress play an important role in the pathogenesis of all phases of atherosclerosis and atherosclerotic plaque rupture which are the main mechanisms in the pathophysiology of acute ST-segment Elevation Myocardial Infarction (STEMI). Acute inferior STEMI is associated with increased in-hospital morbidity and mortality particularly among patients with coexisting Right Ventricular (RV) involvement. High Neutrophil to Lymphocyte Ratio (NLR) is an independent predictor of major adverse cardiac events and mortality in patients with myocardial infarction.

Aim of Study: To study the relationship between the NLR and RV Dysfunction (RVD) in patients with inferior STEMI who underwent primary Percutaneous Coronary Intervention (PCI) or received fibrinolytic therapy. RVD measured by Tricuspid Annular Plane Systolic Excursion (TAPSE) <16 mm and Tissue Doppler Imaging (TDI) S wave <10cm/s [1].

Patients and Methods: This study was conducted on sixty patients diagnosed with acute inferior STEMI and underwent primary PCI or received fibrinolytic therapy in Tanta University Hospitals, Cardiovascular Department, from December 2017 to June 2018. The cases were divided into two groups according to the presence of RVD or not. The groups were compared according to NLR and Receiver Operating Characteristic (ROC) analysis was performed to access the predictability of high NLR in patients with RVD.

Results: The NLR was significantly higher in the group with RVD compared to that without RVD (p=0.002). In ROC analysis, NLR >3.2 predicted RVD with sensitivity of 82.16% and specificity of 89.19%. In a multivariate regression analysis, NLR remained an independent predictor of RVD (95% C.I 0.787-0.976, p=0.002).

Conclusion: NLR was an independent predictor of RVD in patients with acute inferior STEMI who underwent primary PCI or received fibrinolytic therapy.

Key Words: Neutrophil – Lymphocyte Ratio – ST-Segment elevation myocardial infarction.

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Introduction

ISCHAEMIC heart disease is the most common cause of death and its frequency is increasing [2]. The primary goal in management of acute ST-segment Elevation Myocardial Infarction (STEMI) is reperfusion therapy with intravenous fibrinolysis or Primary Percutaneous Intervention (PCI) [3]. Autopsy findings showed that RV involvement is observed in up to 50% of patients with inferior STEMI [4]. Acute inferior STEMI is associated with increased in-hospital morbidity and mortality particularly among patients with coexisting RV dysfunction [1-5]. Inflammation plays an important role in the pathogenesis and progression of the atherosclerosis [6]. The Neutrophil to Lymphocyte Ratio (NLR) shows balance between neutrophil and lymphocyte levels and can be used as an indicator of systemic inflammation. High NLR is a predictor of major adverse cardiac events and mortality in patients with acute Myocardial Infarction (MI) [7].

Aim of the work: Was to assess the relationship between NLR and systolic RVD in patients with acute inferior STEMI who underwent primary PCI or received fibrinolytic therapy.

Patients and Methods

The study included 60 patients diagnosed with acute inferior STEMI according to recent 2017 European Society of cardiology guidelines [2] and presenting to the Cardiology Department at Tanta University Hospital. All patients underwent primary PCI or received fibrinolytic therapy. The study was done in a period of six months starting from December 2017 to June 2018. The included cases were divided into two groups according to RVD

measured by TAPSE and TDI S wave: Group 1 comprised 37 patients in whom patients had normal RV function, (TAPSE >16mm and TDI S wave >10cm/s) and Group 2 comprised 23 patients in whom patients had RVD, (TAPSE <16mm and TDI S wave <10cm/s) [1]. Total and differential White Blood Cells (WBCs) count and echocardiography were done to all patients during admission.

Comparison between the two groups was done during hospitalization according to age, sex, risk factors as Diabetes Mellitus (DM), Hypertension (HTN), smoking, dyslipidaemia, laboratory findings as WBCs count with differentiation (total leucocytic count, neutrophil count, lymphocyte count, neutrophil to lymphocyte ratio), echocardiographic findings (Left Ventricle (LV) ejection fraction, RV mid-way diameter) and type of reperfusion (primary PCI or fibrinolytic therapy).

Exclusion criteria: Included patients with prior myocardial infarction, patients who previously underwent Coronary Artery Bypass Graft (CABG) or PCI, patients with end stage renal failure (creatinine clearance <15mL/min), patients with hematological disorders, patients with active hepatobiliary disease, patients with active infections, patients with neoplastic diseases and patients with recent major surgical procedure or trauma.

Duration of the study: This study was done in a period of six months starting from December 2017 to June 2018.

Statistical analysis:

Data were fed to the computer and analyzed using IBM SPSS software package Version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. Student *t*-test for normally distributed quantitative variables, to compare between two studied groups. ROC analysis was performed to select cut-off values with suitable sensitivity and specificity to detect factor affecting RV function. Univariate and multivariate analysis were performed to investigate the possible predictive factor affecting RV function.

Results

Patient demographics:

Twenty two patients (40%) of the study population were males and 36 patients (60%) were females. There was no statistically significant difference between the both groups (*p*-value= 0.914).

The age of the study population ranged from 31 to 78 years. The age of patients in Group I ranged from 31.0 to 74.0 years, with a mean age of 55.49±11.32 years, while in Group II the age ranged from 35.0 to 78.0 years with a mean ± SD age of 54.70±11.98 years. There was no statistically significant difference between both groups regarding age (*p*-value=0.798).

Prevalence of risk factors:

Table (1) show the prevalence of risk factors in the studied groups. There was no statistically significant difference between both groups.

Type of therapy: Fourteen patients (37.8%) received fibrinolytic therapy, while primary PCI was done for 23 (62.2%) patients in Group I, while 8 patients (34.8%) received fibrinolytic therapy. Primary PCI was done for 15 patients in Group II (65.2%). There was no statistically significant difference between both groups (*p*-value=0.811) (Table 1).

Table (1): Comparison between the two studied groups according to risk factors and type of reperfusion.

	Group I (n=37)		Group II (n=23)		χ^2	p
	No.	%	No.	%		
Hypertension:						
No	20	54.1	8	34.8	2.116	0.146
Yes	17	45.9	15	65.2		
Diabetes Mellitus:						
No	21	56.8	11	47.8	0.455	0.500
Yes	16	43.2	12	52.2		
Smoker:						
No	19	51.4	12	52.2	0.004	0.951
Yes	18	48.6	11	47.8		
Dyslipidemia:						
No	17	45.9	9	39.1	0.268	0.604
Yes	20	54.1	14	60.9		
Type of reperfusion:						
Fibrinolytic	14	37.8	8	34.8	0.057	0.811
pPCI	23	62.2	15	65.2		

Laboratory parameters: Table (2):

The neutrophil count ranged from 2418.0 to 9300.0cell/mm^3 with a mean count of 5349.70± 1792.27cell/mm^3 in Group I, while the neutrophil count ranged from 3392.0 to 11234.0cell/mm^3 with a mean count of 7101.87±1911.84cell/mm^3 in Group II. Neutrophil count was statistically significant higher in Group II than Group I (*p*-value=0.001).

The lymphocyte count ranged from 645.0 to 4080.0cell/mm^3, with a mean count of 2333.03± 977.71 cell/mm^3 in Group I, while the Lymphocyte

count ranged from 1014.0 to 3920.0cell/mm^3, with a mean count of 1958.83 ±759.98cell/mm^3 in Group II. There was no statistically significant difference between both groups (*p*-value=0.136).

The TLC count ranged from 3900 to 12600 cell/mm^3, with a mean count of 8130±2460 cell/mm^3 in Group I, while the TLC count ranged from 5300 to 13700cell/mm^3, with a mean count of 9570 ±2030cell/mm^3 in Group II. TLC count was statistically significant higher in Group II than Group I (*p*-value=0.021).

The N/L Ratio ranged from 1.0 to 8.50, with a mean of 2.68±1.52 in Group I, while the N/L Ratio ranged from 1.57 to 6.90, with a mean of 4.08± 1.65 in Group II. NLR was statistically significant higher in Group II than Group I (*p*-value=0.002) (Table 2).

Table (2): Comparison between both groups according to laboratory parameters.

	RV Dysfunction		Test of sig.	*p*
	Group I (n=37)	Group II (n=23)		
Neutrophil count (cell/mm^3):				
Min.-max.	2418.0-9300.0	3392.0-11234.0	*t=*	0.001*
Mean ± SD.	5349.70±1792.27	7101.87±1911.84	3.589*	
Median	5183.0	6800.0		
Lymphocyte count (cell/mm^3):				
Min.-max.	645.0-4080.0	1014.0-3920.0	U=	0.136
Mean ± SD.	2333.03±977.71	1958.83±759.98	327.50	
Median	2280.0	1728.0		
NLR:				
Min.-max.	1.0-5.33	1.70-8.50	U=	0.001*
Mean ± SD.	2.31±1.0	4.68±1.59	101.0*	
Median	2.10	5.0		
TLC count (cell/mm^3):				
Min.-max.	3.90-12.60	5.30-13.70	*t=*	0.021*
Mean ± SD.	8.13±2.46	9.57±2.03	2.366*	
Median	8.30	9.70		

t : Student *t*-test.
U : Student *t*-test.
p : *p*-value for comparing between Normal RV function and RVD.
* : Statistically significant at *p*≤0.05.
NLR : Neutrophil to Lymphocyte Ratio.
Min : Minimum.
Max : Maximum.
SD : Standard Deviation.

Echocardiographic findings: Table (3):

The EF ranged from 49.0 to 72.0% with a mean of 58.16±4.62% in Group I, while the EF ranged from 45.0 to 66.0%, with a mean of 53.30±5.39% in Group II. EF was statistically significant lowered in Group II than Group I (*p*-value=0.001).

The RV mid-way diameter ranged from 23.0 to 34.0mm, with a mean of 27.03 ±2.65mm in Group I, while the RV mid-way diameter ranged from 24.0 to 33.0mm, with a mean of 28.83 ± 2.92mm in Group II. RV mid-way diameter was statistically significant larger in Group II than Group I (*p*-value=0.017).

The left atrium size ranged from 3.20 to 4.60 cm with a mean of 3.86±0.39cm in Group I, while the (LA) size ranged from 3.0 to 4.50cm with a mean of 3.86±0.37cm in Group II. (*p*-value=0.956). There was no statistically significant difference between both groups (Table 3).

Table (3): Comparison between the two studied groups according to echocardiographic parameters.

	Patient population=60		*t*	*p*
	Group I (n=37)	Group II (n=23)		
EF (%):				
Min.-max.	49.0-72.0	45.0-66.0	3.716*	0.00 1 *
Mean ± SD.	58.16±4.62	53.30±5.39		
Median	58.0	53.0		
RV mid-way diameter (mm):				
Min.-max.	23.0-34.0	24.0-33.0	2.459*	0.017*
Mean ± SD.	27.03±2.65	28.83±2.92		
Median	27.0	29.0		
LA size (cm):			0.055	
Min.-max.	3.20-4.60	3.0-4.50		0.956
Mean ± SD.	3.86±0.39	3.86±0.37		
Median	4.0	4.0		

t : Student *t*-test.
p : *p*-value statistically significant at *p*≤0.05.

Univariate and multivariate analysis for the parameters affecting RV dysfunction:

Univariate and multivariate analysis were performed to investigate the possible predictive factor affecting RVD. In univariate analysis, sex, age, HTN, DM, smoking, dyslipidemia, neutrophil count, lymphocyte count, N/L ratio, TLC count, EF, RV midway diameter and LA size were correlated with RVD (Table 4).

In the multivariate analysis, using model adjusted for previously mentioned parameters, (neutrophil count, N/L ratio, TLC count, EF and RV mid-way diameter) independently predicted RVD.

The Receiver Operating Characteristic (ROC) analysis showing the performance and predictive accuracy of N/L ratio in prediction of right ventricular dysfunction; AUC was 0.881with cut off value of NLR >3.2, with 82.61% sensitivity and 89.19% specificity.

Table (4): Univariate and multivariate analysis for the parameters affecting dysfunction (n=60).

	Univariate		#Multivariate	
	p	OR (95%C.I)	*p*	OR (95%C.I)
• Sex (female)	0.914	1.061 (0.366-3.073)		
• Age (years)	0.794	0.994 (0.950-1.040)		
• Hypertension	0.149	2.206 (0.753-6.459)		
• Diabetes mellitus	0.501	1.432 (0.503-4.072)		
• Smoker	0.951	0.968 (0.341-2.742)		
• Dyslipidaemia	0.605	1.322 (0.459-3.809)		
• Neutrophil count (cell/mm3)	0.002*	1.001 (1.000-1.001)	0.223	0.998 (0.996-1.001)
• Lymphocyte count cell/mm3	0.126	1.000 (0.999-1.000)		
• Neutrophil to Lymphocyte Ratio (NLR)	<0.001*	3.462 (1.957-6.127)	0.013*	5.208 (1.424-19.054)
• TLC count (cell/mm3)	0.027*	1.324 (1.032-1.697)	0.136	4.710 (0.613-36.193)
• Ejection fraction (EF) (%)	0.002*	0.809 (0.707-0.925)	0.092	0.830 (0.669-1.031)
• Right ventricle mid-way diameter (mm)	0.022*	1.267 (1.035-1.551)	0.890	1.025 (0.727-1.445)
• Left atrium size (cm)	0.955	0.961 (0.243-3.805)		
• Number of vessels	0.205	1.427 (0.823-2.472)		

OR: Odd's ratio.　　　　　C.I: Confidence Interval.
All variables with *p*<0.05 was included in the multivariate.
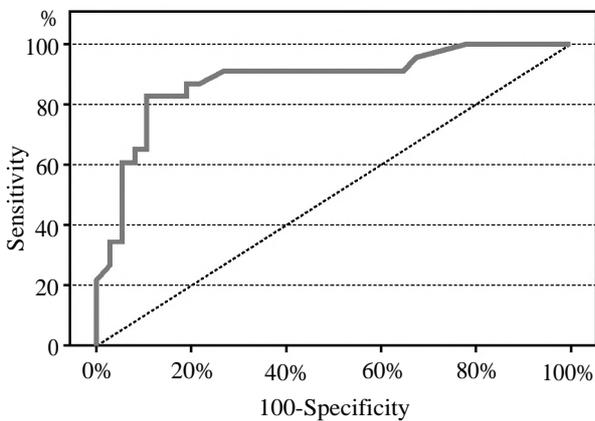
	NLR
AUC	0.881
p	0.001*
95% C.I	0.787-0.976

ROC curve for N/L ratio to predict RV dysfunction.
AUC : Area Under a Curve.
p-value : Probability value.
CI : Confidence Intervals.

	Cut off Sensitivity	Specificity	PPV	NPV
NLR >3.2	82.61	89.19	82.61	89.19

PPV: Positive Predictive Value. NPV: Negative Predictive Value.

Discussion

Ischemic heart disease is the most common leading cause of death worldwide and its frequency is increasing [2]. Recent studies have demonstrated a better prognosis following STEMI with greater use of reperfusion therapy, primary PCI, modern antithrombotic therapy, and secondary prevention [8]. Atherosclerosis and atherosclerotic plaque rupture are the main causes of STEMI. Inflammation plays an important role in formation of atherosclerosis and may lead to plaque rupture in the presence of several risk factors [9]. Several factors involve impairment of perfusion at tissue level after STEMI. These are white blood cell and platelet accumulation in capillaries, inflammation-driven complex neutrophil and platelet interactions, reactive oxygen radicals, distal thrombus embolization, and endothelial dysfunction due to ischemia and reperfusion injury. Inflammation has a substantial contribution to this process. It has also a negative effect on myocardial function. Response of white blood cells to different inflammatory triggers leads to secretion of pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6, and C-reactive protein. By the effects of these cytokines, contractile function of myocardium may decrease [10].

Neutrophils also secrete several proteolytic enzymes such as myeloperoxidase, acid phosphatase, and elastase which help destroying tissue structure, and neutrophil-driven microvascular obstruction can worsen ischemia and lead infarct expansion, as well [11].

Studies reported that lymphocytopenia was independently associated with mechanical complications and mortality in patients with acute STEMI [12].

As regard age and sex in our study there was no significant difference between the two groups as regarding age (*p*-value=0.798) and sex (*p*-value =0.914).

In our study most of the patients that presented with acute STEMI were females 36 patients (60%), as regarding 2017 ESC guidelines ischemic heart disease develops on average 7-10 years later in women compared with men, MI remains a leading cause of death in women. Acute Coronary Syndrome (ACS) occurs three to four times more often in men than in women below the age of 60 years, but after the age of 75, women represent the majority of patients [13].

Regarding the neutrophil count:

In this study there was a statistically significant difference between the two groups. Neutrophil count was higher in RV dysfunction group than normal RV function group, with p-value=0.001.

In concordance with the result of our study is the study conducted by Yaylak et al., [14], showed that neutrophil count was higher in Group II than Group I with p-value=0.003.

Regarding the TLC count:

In this study there was a statistically significant difference between the two groups. TLC count was higher in the RV dysfunction group than the other group, with p-value=0.021.

In contrast with the result of our study is the study conducted by Yaylak et al., [14], showed that there was no statistically significant difference between the two groups with p-value=0.007.

Regarding the NLR:

In this study there was a statistically significant difference between the two groups. N/L Ratio was higher in patients with RV dysfunction group than patients with normal RV function group, with p-value=0.002.

In concordance with the result of our study is the study conducted by Yaylak et al., [14], showed that NLR was higher in patients in Group II than Group I with p-value=0.001.

Regarding the LV ejection fraction (EF):

In this study there was a statistically significant difference between the two groups as patients with RVD showed lowered EF than patients with normal RV function, with p-value=0.001.

In concordance with the result of this study is the study conducted by Rajesh et al., [15] with p-value=0.05 and Park, S.J et al., [16] with p-value =0.001.

In contrast with the result of this study is the study conducted by Yaylak et al., [14], Altintas et al., [17], Kanar et al., [18], who showed no statistically significant difference between both groups in EF.

Regarding RV midway diameter:

In our study there was a statistically significant difference between the two groups as patient with RV dysfunction showed larger RV midway diameter than patients with normal RV function, with p-value=0.017.

In contrast with the result of this study is the study conducted by Altintas et al., [17], Kanar et al., [18] and Smarz et al., [19], who showed no statistically significant difference between both groups regarding RV midway diameter.

Limitations of the study:

The study had some limitations. This is a single-center experience and represents a limited number of patients.

Duration of the study was relatively short.

Conclusion:

Neutrophil to lymphocyte ratio was an independent predictor of RVD in patients with acute inferior STEMI undergoing primary PCI or received thrombolytic therapy.

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العلاقة بين نسبة الخلايا متعادلة التأثير الصبغى
إلى الخلايا الليمفاوية والخلل الوظيفى الإنقباضى للبطين الأيمن
فى مرضى الإحتشاء السفلى الحاد لعضلة القلب

يعد الإحتشاء القلبى الحاد واحداً من آهم آمراض القلب وسبب رئيسى للمرض والوفاة والهدف الآول والآهم فى العلاج هو إعادة الإرواء السريع إما عن طريق آدوية إذابة الجلطات آو إجراء القسطرة القلبية العلاجية.

أثبتت الدراسات آن ٥٠٪ من حالات الإحتشاء السفلى لعضلة القلب تتأثر فيها وظيفة البطين الآيمن وينتج عن ذلك زيادة فى معدلات الوفاة. وما زالت الموجات فوق الصوتية على القلب هى حجر الآساس فى تقييم وظيفة البطين الآيمن.

الإلتهاب والآكسدة يلعبان دوراً رئيسياً فى آمراض تصلب الشرايين والتى تعد بدورها السبب الرئيسى فى إحتشاء عضلة القلب وقد تبين آن كثير من الخلايا الإلتهابية لها دور فى تصلب الشرايين وآن الخلايا متعادلة التأثير الصبغة والخلايا الليمفاوية تعد من آهم الخلايا المتسببة فى التصلب.

وقد كان الهدف من هذا البحث هو: دراسة العلاقة بين نسبة الخلايا متعادلة التأثير الصبغى إلى الخلايا الليمفاوية والخلل الوظيفى الإنقباضى للبطين الآيمن فى المرضى الذين يعانون من إحتشاء سفلى بعضلة القلب والذين خضعوا للقسطرة العلاجية الآولية للشرايين التاجية آو الذين تم إعطائهم عقار مذيب للجلطة.

المرضى وطرق البحث: آجريت هذه الدراسة على ستين مريضاً آصيبوا بجلطة حادة فى الشريان التاجى وتمت المعالجة عن طريق القسطرة العلاجية الآولية على الشرايين التاجية آو تم إعطائهم عقار مذيب للجلطة فى مستشفى جامعة طنطا فى الفترة من ديسمبر ٢٠١٧ حتى نهاية يونيو ٢٠١٨.

معايير الإدراج: مرضى الإحتشاء السفلى الحاد لعضلة القلب والذين تم علاجهم بالقسطرة القلبية العلاجية الآولية على الشرايين التاجية آو تم إعطائهم عقار مذيب للجلطة.

معايير الإستبعاد:
• المرضى المصابون من قبل بإحتشاء حاد فى عضلة القلب.
• الفشل الكلوى بالمرحلة النهائية.
• آمراض الدم والكبد والقنوات المرارية.
• المرضى الذين يعانون من عدوى نشطة.
• الآمراض السرطانية والذين تعرضوا حديثاً لجراحة آو حادث كبير.

تم تقسيم المرضى إلى مجموعتين طبقاً للكفاءة الوظيفيية الإنقباضية للبطين الآيمن للقلب:
• المجموعة الآولى: ٣٧ مريض ذو كفاءه وظيفية إنقباضية طبيعية للبطين الآيمن للقلب.
• المجموعة الثانية: ٢٣ مريض ذو خلل فى الكفاءة الوظيفية الإنقباضية للبطين الآيمن للقلب.

خضع كل المرضى الذين آجريت عليهم الدراسة إلى إستيفاء التاريخ المرضى الكامل للحالة، عمل فحص إكلينيكى كامل للحالة، عمل رسم قلب، عمل موجات فوق صوتية على القلب، إجراء بعض التحاليل بالدم ومن ضمنها صورة الدم الكاملة ونسبة الدهون الثلاثية والكوليسترول، إجراء قسطرة علاجية آولية على الشرايين التاجية آو إعطاء العقار المذيب للجلطة ومتابعة المريض آثناء تواجده بالمستشفى.

وقد خلصت هذه الدراسة إلى آن إرتفاع نسبة الخلايا متعادلة التأثير الصبغى إلى الخلايا الليمفاوية صاحبه خلل فى الكفاءه الوظيفية الإنقباضية للبطين الآيمن للقلب فى المرضى الذين يعانون من إحتشاء سفلى بعضلة القلب والذين خضعوا للقسطرة العلاجية الآولية للشرايين التاجية آو الذين تم إعطائهم عقار مذيب للجلطة.