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Original Article

Internal Medicine Section

Association between Coronary Artery Ectasia and Neutrophil: Lymphocyte Ratio

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ABSTRACT

Introduction: Inflammation, endothelial dysfunction and atherosclerosis are associated with the aetiopathogenesis of Coronary Artery Ectasia (CAE). The Neutrophil to Lymphocyte (N/L) ratio has emerged as a new inflammation marker for cardiovascular disease.

Aim: To assess the association between the CAE and the N/L ratio.

Materials and Methods: A total of 179 patients with isolated CAE, Obstructive Coronary Artery Disease (O-CAD) and normal coronaries (controls) were enrolled. Clinical characteristics and pattern of ectatic involvement were seen. N/L ratio values were compared between the three groups using Analysis of Variance (ANOVA).

Results: Study findings showed that the patients with isolated CAE had significantly elevated N/L ratio values compared to O-CAD and control groups (2.63±0.36 vs. 2.20±0.27, p<0.001 and vs. 1.93±0.24, p<0.001) respectively. Right Coronary Artery (RCA) was the most commonly involved ectatic artery (64.2%). Single vessel ectasia (44.6%) and Type IV (32.1%) were the most common pattern of involvement.

Conclusion: In present study, we found that patients with isolated CAE had a significantly higher WBC count and N/L ratio than patients with O-CAD and control groups. This finding suggests that severe inflammatory process could be involved in the development of CAE as compared to CAD.

Keywords: Atherosclerosis, Coronary artery disease, Inflammation

INTRODUCTION

Coronary artery ectasia is a well-recognised yet uncommon abnormality of the coronary anatomy. It is defined as localised or diffuse dilation of >1.5 times normal adjacent segments of vessels [1,2]. Isolated CAE refers to ectasia without atherosclerosis. About 20-30% of cases of coronary ectasia are considered congenital and the rest are acquired. In clinical practice, atherosclerosis is responsible for being the single most important acquired cause while rest are associated with inflammatory and connective tissue diseases and bacterial infections [3]. It is well-known that atherosclerosis is an inflammatory process, as confirmed by recent studies of atherosclerosis focusing in particular on the role of chemokines in atherosclerotic leukocyte accumulation [4]. The coronary slow flow phenomenon has also been seen in patients with CAE, indicating that endothelial dysfunction is involved and that there is a link to subclinical atherosclerosis or inflammation [5]. However, the exact links between inflammatory mediators and CAE remain to be evaluated.

Recent evidences have also revealed that some specific subtypes of leukocytes have higher predictive value in assessing the cardiovascular risk. Such value is even higher when N/L ratio is used [4,5]. The N/L ratio has emerged as a new inflammation marker. Although N/L ratio is a predictor of long-term cardiovascular risk [6-8], its importance in the presence of isolated CAE has not been evaluated in Indian population to best of our knowledge. Thus, we aimed at evaluating the association between CAE and N/L ratio.

MATERIALS AND METHODS

An observational prospective study was conducted with patients over 18 years of age who had been admitted for evaluation of suspected CAD in the tertiary hospital, NEIGRIHMS, Shillong, Meghalaya, India, in the period between November, 2014 and November, 2016. This study had been approved by Institute Medical Ethical Committee. Written consents were taken from all the patients.

This study consist of three different group of population on the basis of coronary angiography findings, in which group A, B and C consist of isolated CAE patients, obstructive coronary artery disease patients and normal coronaries i.e., control group respectively. Group A, B and C had 56, 58 and 65 patients respectively. The estimated sample size was calculated using the formula,

$$n=4pq/d^2$$

where, p (prevalence) =10%; q=1-p, d (standard error=5%) which yielded a required sample of 71. However, due to constraints of time the total number of patients in each group was 56, 58 and 65 respectively.

Patients with active infection, liver disease, renal failure, alcoholism, leukaemia, lymphoma, haemolytic anaemia, receiving chemotherapy and radiation treatment, severe valvular heart disease, non O-CAD and O-CAD with ectasia on angiogram were excluded from study.

The patient clinical characteristics including age, sex, smoking status, diabetes mellitus, and hypertension were recorded. All the routine blood investigation including differential leukocyte count was done followed by echocardiography and coronary angiogram. Indication for CAG was either the presence of typical angina or positive result of treadmill test for myocardial ischaemia. These groups were compared for clinical characteristics and N/L ratio. Peripheral venous blood samples were drawn after overnight fasting. Total and differential leukocyte counts were measured using an automated haematology analyser.

Coronary Angiogram Assessment

Selective CAG was performed predominantly by radial route in multiple projections without the use of nitroglycerin or any other coronary epicardial dilator like adenosine and calcium channel blocker. CAGs were analysed by three experienced angiographers who were blinded to patient clinical and haemotological profile. The vessel diameter was calculated quantitatively in case of conflicts about CAE. The severity of isolated CAE was determined according

to the Markis classification [1]. In decreasing order of severity, it classifies Type I as diffuse ectasia in at least two vessels, Type II as diffuse ectasia in one vessel and discrete ectasia in another vessel, Type III as diffuse ectasia in only one vessel without any evidence of ectasia in other vessels and Type IV as only discrete ectasia involving vessel. CAD was defined as stenosis of more than 50% of the diameter in one or more major epicardial artery.

STATISTICAL ANALYSIS

SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables were expressed as Mean±Standard Deviation (SD). Categorical variables were expressed as percentages. Group means for continuous variables were compared with ANOVA Categorical variables were compared with the chi square test. F ratio was measured which is a statistical term named after scientist Ronald A Fischer. A p-value of ≤0.05 was considered statistically significant.

RESULTS

The study population consisted of 179 patients. The mean age of the patients in Group A, B and C was 53.72±4.9, 56.15±7.3 and 53.25±8.4 years respectively. The patients with isolated CAE were relatively younger as compared to O-CAD. Male gender constituted 106 (59.2%) of the total patients. We found that isolated CAE were most likely to occur in right coronary artery 36 (64.2%) closely followed by 34 (60.7%) in Left Anterior Descending (LAD) coronary artery, less commonly Left Circumflex Artery (LCX) was involved 26 (46.4%) and mostly involved single vessel 25 (44.6%). According to the Markis classification, Type 4 (32.1%) was the most common types of isolated CAE [Table/Fig-1].

Parameters	Group A (CA Ectasia) N (56)	Group B (CAD) N (58)	Group C (Normal CAG) N (65)	p-value
Age (years)	53.72±4.9	56.15±7.3	53.25±8.4	0.07
Male/Female (Male%)	31/25 (55.3%)	33/25 (56.8%)	42/23 (65%)	0.12
Hypertension	29 (51.7%)	32 (55.1%)	30 (46.1%)	0.59
Diabetes Mellitus	16 (28.5%)	20 (34.4%)	24 (36.9%)	0.61
Smoker	20 (35.7%)	24 (41.3%)	26 (40.0%)	0.81
Family history of myocardial infarction	9 (16.0%)	8 (13.7%)	6 (9.2%)	1.12
History of Myocadial infarction	02	12	0	<0.01
Total leukocyte count	8.06±1.26	7.30±1.49	6.45±1.17	<0.001
Neutophil/lymphocyte (N/L) ratio	2.63±0.36	2.20±0.27	1.93±0.24	<0.001
LVEF (Left Ventricle Ejection Fraction)	58.64	53.15	57.78	<0.01
Ectatic arteries-				
Single Vessel Disease (SVD)	SVD ectatic -25 (44.6 %)			
Double Vessel Disease (DVD)	DVD ectatic -22 (39.2 %)			
Triple Vessel Disaese (TVD)	TVD ectatic -09 (16.2%)			
Left Anterior Descending Coronary Artery (LAD)	LAD -34 (60 .7%)			
Left Circumflex Coronary Artery (LCX)	LCX -26 (46.4%)			
Right Coronary Artery (RCA)	RCA -36 (64.2%)			
	Type 1 -12 (21.4 %)			
	Type 2 -15 (26.7 %)			
	Type 3 -11 (19.6 %)			
	Type 4 -18 (32.1 %)			

[Table/Fig-1]: General characteristics of different groups.

It was found that there were no significant differences between the groups with reference to hypertension, Type 2 diabetes mellitus, dyslipidemia, and smoking status (p>0.05). The LVEF however was lower in Group B and was statistically significantly different from the other two groups (p<0.01).

The mean WBC count and N/L ratio was found to be higher in both the CAE as well as the CAD group in comparison to the control group. Patients with CAE had a higher mean WBC count and N/L ratio than patients with CAD [Table/Fig-1].

On comparing the groups using ANOVA, statistically significant difference was found in WBC count between the CAE, CAD and control groups with F ratio of 22.16 and a p-value of <0.001 [Table/Fig-2]. Similarly statistically significant difference was found in N/L ratio between the CAE, CAD and control groups with an F ratio of 79.79 and a p-value of <0.001 [Table/Fig-3].

Source	SS	Df	MS	F ratio	p-value
Between groups	77.62	2	38.31	22.16	<0.001
Within groups	299.04	173	1.72		
Total	375.66	175			

[Table/Fig-2]: Comparison of WBC count in different subgroups with analysis of variance.
* SS: Sum of squares; **MS: Mean square; df: Degrees of freedom

Source	SS	Df	MS	F ratio	p-value
Between groups	14.22	2	7.11	79.79	<0.001
Within groups	15.42	173	0.08		
Total	29.65	175			

[Table/Fig-3]: Comparison of N/L in different subgroups with analysis of variance.

DISCUSSION

In this study, we found that there were statistically significant increased mean levels of total leukocyte count as well as ratio of N/L in patients with coronary ectasia and O-CAD as compared to normal coronaries (p<0.01). There was also statistically significant increased WBC count and N/L ratio in CAE as compared to O-CAD (p<0.01).

Balta S et al., in their study, found a higher N/L ratio in the CAE and O-CAD groups compared to the control group [9], They reported no difference between CAE and O-CAD groups however, there was statistically significant difference in CAE and CAD as compared to normal coronaries patients. However, Kalaycıoğlu E et al., reported significant difference between CAE and O-CAD [10]. CAE group had higher WBC count and N/L ratio as compared to O-CAD and NCA, similar to findings of present study. Thus in the present study, N/L ratio was associated with the increased likelihood of isolated CAE. Therefore, CAE may be related to more severe inflammation when compared to O-CAD and control groups.

The medial layer of the vascular wall contains a well arranged layer of smooth muscle with extracellular matrix proteins like elastin and collagen, which forms a structure that maintains vascular wall integrity [11]. The extensive destruction of this important medial layer of the vessel wall in the ectatic segment has been reported in postmortem histopathologic studies. Infiltration of the media layer by inflammatory cells is significant finding that can be seen in ectatic segments [12]. Markis JE et al., stated that the destruction of the vascular media as the principal cause of ectasia [1].

Previous studies have reported that Neutrophil Elastase (NE), a serine proteinase, may play a crucial role in the aetiopathogenesis of CAE [12]. NE is predominantly present in neutrophils and can digest vascular medial layer content namely elastin, collagen and proteoglycans. Akyel A et al., found that higher Neutrophil Gelatinase-Associated Protein (NGAL) levels were detected in patients with CAE compared to those with normal coronaries [13]. NGAL prevents degradation of MMP-9 which has a role in the degradation of collagen. Therefore, NE or NGAL may explain the relationship between N/L ratio and CAE.

The association between inflammation and CAE was evaluated based on the findings of previous postmortem studies. Higher

levels of Interleukin-6 (IL-6) [14], Matrix Metalloproteinase-3 (MMP-3) [15], high sensitivity (hs-CRP) [16] have been seen in patients with isolated CAE, compared to patients with O-CAD. Additionally, Kocaman SA et al., also reported that patients with isolated CAE had significantly higher leukocyte and neutrophil levels than patients with non O-CAD and normal coronaries [17]. Yilmaz H et al., reported that patients with isolated CAE have raised levels of plasma soluble Intercellular Adhesion Molecule-1 (ICAM-1) [18], E-selectin and Vascular Cell Adhesion Molecule-1 (VCAM-1) in comparison to patients with O-CAD and normal coronaries.

Studies in the recent past have reported that elevated levels of inflammatory indicators are markers of atherosclerotic disease activity and also indicate an increased risk of the progression of atherosclerosis [19]. Although the underlying mechanism of abnormal luminal dilatation is not well known, yet the histopathological characteristics of CAE are similar to those of coronary atherosclerosis. Leukocyte subtype and N/L ratio are also indicators of systemic inflammation [6,7]. These markers have prognostic value in cardiovascular disease. Zazula AD et al., found N/L ratio was significantly higher in patients in acute coronary syndrome patients compared to patients diagnosed with non cardiac chest pain [20]. The N/L ratio levels give information about CAD severity in patients with acute myocardial infarction [21]. Because of all of these findings from previous studies, aetiology of the relationship between N/L ratio and CAE may be inflammation and atherosclerosis. N/L ratio may appear additive to conventional risk factors and commonly used biomarkers. In addition, interestingly, the N/L ratio has remained as a predictor of all-cause mortality in patients with normal WBC counts [22].

CAE can be identified by more sensitive and specific cardiovascular imaging tools. However, these tools are expensive and with ill effects such as exposure to radiation. Therefore, N/L ratio, which is low cost and readily done blood test, can be used as an initial filter criteria, and will help in determining the need for further imaging modalities in the assessment of CEA.

LIMITATION

Major limitation of the study was small number of patients which may limit the generalisability of our findings. Secondly, it didn't study the correlation of N/L ratio with short and long-term events. Thirdly, it did not assess the predictive value of other inflammatory markers such as CRP, TNF-α and IL-6. Lastly, the pathological role of elevated WBC and N/L ratio in patients of CAE has not been shown, so association may not prove causality. These issues should be addressed by large scale studies in future.

CONCLUSION

This study shows that a more severe inflammatory process may be involved in the development of CAE as compared to O-CAD. This severe involvement leads to abnormal dilatation of coronary artery by damaging its medial layer rather than causing stenotic lesion. To conclude, N/L ratio may be turned into a valuable parameter for the preliminary approach of patients with suspicion of CAD to rule out CAE.

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