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**Original Article,**

# The Relationship between the Angiographic Atherosclerotic Burden and the Inflammatory Factors in Diabetic and Non-Diabetic Patients with Coronary Artery Disease

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**Abstract:**

**Objective:** Inflammation is a known pathophysiological feature that is common in both diabetes mellitus (DM) and atherosclerosis. High-density lipoprotein (HDL) is an anti-atherogenic lipoprotein and has an inverse relationship with coronary artery disease (CAD). In the present study, the association between the severity of CAD and inflammatory parameters neutrophil to HDL (NHR), lymphocyte to HDL (LHR), and platelet to HDL (PHR) was investigated.
**Methods:** In this single-center prospective study, 98 diabetic (type 2 DM), and 320 non-diabetic CAD patients who underwent coronary angiography were enrolled. Baseline demographic characteristics were recorded, hematologic and biochemical samples were measured, the angiographic profile was analyzed, SYNTAX and Gensini scores were calculated for all patients.
**Results:** Hypertension and smoking rates and HbA1c were higher in the diabetic group (p:0.001, p<0.001, p<0.001, respectively). NHR, LHR, and PHR were significantly higher in the diabetic group compared with the non-diabetic group (p:0.007, p:0.002, p:0.005, respectively). The diabetic group had higher SYNTAX and Gensini scores (p<0.001 for both). NHR, LHR, PHR, age, and hemoglobin were positively correlated with both SYNTAX and Gensini scores in the correlation analysis. Univariate and multivariate analyses showed that NHR, LHR, SYNTAX and Gensini scores were found to be independent predictors of DM in CAD patients.
**Conclusion:** Our study demonstrated that the inflammatory parameters NHR, LHR, and PHR and atherosclerotic burden parameters SYNTAX and Gensini scores were worsening in diabetic patients. NHR, LHR, and PHR were significantly associated with higher SYNTAX and Gensini scores in diabetic and nondiabetic patients.

**Keywords:** neutrophil, lymphocyte, platelet, high-density lipoprotein, SYNTAX, Gensini

## Introduction:

Coronary artery disease (CAD) patients who also have type 2 diabetes mellitus (DM) have a higher burden of coronary atherosclerosis (1, 2). In addition, these patients have a higher rate of cardiovascular events and a lower rate of therapeutic response (3, 4). Diabetic metabolic disorder initiates and progresses atherosclerosis and atherothrombosis by causing endothelial damage and dysfunction (5, 6). Inflammation could be one of the risk factors that contribute to the initiation and progression of atherosclerotic processes by promoting plaque growth (7).

High-density lipoprotein (HDL) is a major lipoprotein that has an inverse relationship with CAD, inhibiting macrophage migration, reducing low-density lipoprotein (LDL) oxidation, promoting the removal of cholesterol efflux from cells, and preventing platelet aggregation (8, 9). On the other hand, blood components such as neutrophils, lymphocytes, platelets, and eosinophils are involved in the atherosclerotic inflammatory process. As known, circulating blood cells interact with endothelial cells and platelets via the secretion of different cytokines and factors, and initiating inflammatory and pro-

thrombotic pathways (10). Neutrophils to lymphocyte ratio and platelet to lymphocyte ratio have been indicated to be inversely associated with HDL in CAD patients (8, 11).

It has been reported that the neutrophils to HDL ratio (NHR) and platelet to HDL ratio (PHR) are associated with the severity of CAD in a previous study (12). However, there is limited data on the relationship of these inflammatory parameters with the severity of CAD and atherosclerosis. Therefore, in this study, we aimed to investigate the relationship between these inflammatory parameters and the severity of CAD in diabetic and non-diabetic patients.

## Materials and methods:

### Study population

A total of 418 consecutive patients with an initial diagnosis of CAD who underwent coronary angiography from September 2022 to May 2023 were enrolled in this prospective study. Patients with either of the following conditions were excluded: type 1 DM, acute myocardial infarction, severe heart failure, congenital heart disease, peripheral artery diseases, autoimmune diseases, malignancies, acute or chronic inflammatory diseases, renal and hepatic dysfunction, rheumatic and infectious diseases, and consumption of immunosuppressive drugs. The patients were divided into two groups. The type 2 diabetic group involved 98 patients and the non-diabetic group involved 320 patients. The diagnosis of type 2 DM was made according to the criteria of the American Diabetes Association (13).

The study was designed and conducted with the approval of the local ethics review commission and in accordance with the Declaration of Helsinki. Informed consent forms were obtained from all patients (Harran University Ethical Committee, date: 05.09.2022, number: HRÜ/22.17.21).

### Coronary angiography analysis:

Coronary angiography was performed and quantitative analysis for the angiographic coronary atherosclerosis severity was conducted by two experienced interventional cardiology specialists who were blinded to the study protocol. The number of vessels, number of percutaneous transluminal coronary intervention, and coronary artery bypass grafting were recorded. The coronary atherosclerosis severity according to the angiography was calculated by SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) and Gensini scores as previously described (14, 15).

### Biochemical and hematological parameters

Blood samples were obtained from the peripheral venous system before coronary angiography in the morning after a 12-hour fasting period. After blood samples were centrifuged serum fasting glucose, creatinine, HDL cholesterol, LDL cholesterol, and triglyceride (TG) were measured with standard laboratory techniques by an automatic biochemical analyzer (BT 3000, auto-analyzer, USA). Hemoglobin A1c was measured using an automatic analyzer (Tosoh automated glycohemoglobin analyzer, Tokyo, Japan). NHR, LHR, and PHR were calculated as neutrophil/lymphocyte/platelet counts divided by HDL cholesterol amount.

### Statistical analysis

Categorical variables were presented as counts and percentages. Continuous variables were evaluated for normal distribution by using the Kolmogorov-Smirnov test and presented as mean (standard deviation) or median with interquartile range. Students't-test was used for normally distributed variables. The chi-square test for categorical variables to assess the differentiation between the groups. Pearson correlation test was used for correlation analysis between SYNTAX, Gensini scores, and other parameters. Univariate and multivariate binary regression analyses were used to define independent predictors of DM. Variables that resulted in a p-value less than 0.10 in univariate analysis were included in the multivariate analysis. A p-value less than 0.05 was accepted as statistically significant. Statistical analysis was performed by using the 20.0 SPSS for Windows (SPSS Inc. Chicago, Illinois, USA).

## Results:

98 type 2 DM patients and 320 non-diabetic patients who underwent coronary angiography were included. Baseline characteristics, laboratory parameters, angiographic data, and clinical features of the patients are shown in Table-1. The rate of smoking and hypertension (HT) was found to be significantly higher in the diabetic group (p:0.001, p<0.001, respectively). Mean HbA1c was 7.2±2.0 and significantly higher in the diabetic group (p<0.001). NHR, LHR, and PHR were significantly higher in the diabetic group compared with the non-diabetic group (p:0.007, p:0.002, p:0.005, respectively).

Compared with the non-diabetic group, the diabetic group had higher SYNTAX and Gensini

scores (p<0.001 for both). Single vessel disease rates were higher in the non-diabetic group, but multivessel disease rates were higher in the diabetic group (p:0.011). LAD was the most frequently occluded vessel in both groups. While the number of patients for whom PTCA was decided was higher in the non-diabetic group, the number of patients whom CABG was decided was higher in the diabetic group (p:0.008).

**Table-1. Baseline clinical, laboratory and angiographic characteristics of Type 2 DM and Non-diabetic groups.**

| Variables | Type 2 DM (n: 98) | Non-DM (n: 320) | p |
|---|---|---|---|
| **Age (years)** | 58.7±11.4 | 56.4±11.9 | 0.086 |
| **Male (n, %)** | 61 (62.2) | 206 (64.3) | 0.824 |
| **BMI (kg/m$^2$)** | 28.5±4.9 | 27.5±3.2 | 0.055 |
| **Smoking (n, %)** | 48 (48.9) | 122 (38.1) | **0.001** |
| **HT (n, %)** | 64 (65.3) | 130 (40.6) | **<0.001** |
| **LDL (mg/dL)** | 117.3±38.2 | 120.6±39.1 | 0.460 |
| **HDL (mg/dL)** | 45.8±11.3 | 47.6±12.1 | 0.183 |
| **TG (mg/dL)** | 151.5±81.7 | 159.5±88.5 | 0.411 |
| **Glucose (mg/dL)** | 175.1±97.6 | 171.0±84.3 | 0.710 |
| **Creatinine (mg/dL)** | 0.99±0.17 | 0.89±0.34 | 0.324 |
| **C-reactive Protein (mg/L)** | 9.2±2.7 | 7.9±2.2 | 0.164 |
| **HbA1c (%)** | 7.2±2.0 | 5.5±1.9 | **<0.001** |
| **Hgb (g/dL)** | 14.8±1.6 | 14.7±1.5 | 0.764 |
| **Leucocyte (µL)** | 12880.2±3042.3 | 11919±3633.4 | 0.116 |
| **Neutrophyl (µL)** | 9280.9±3280.8 | 8899.0±3676.3 | 0.066 |
| **Lymphocyte (µL)** | 2931.8±1503.9 | 2856.7±1605.6 | 0.080 |
| **Platelets (mm$^3$)** | 296989.8±99769.2 | 277275.0±79343.3 | 0.079 |
| **RDW (%)** | 13.5±0.9 | 13.6±1.0 | 0.225 |
| **MPV (fL)** | 7.95±1.1 | 8.1±1.0 | 0.183 |
| **NHR** | 206.9±59.6 | 174.9±47.3 | **0.007** |
| **LHR** | 66.7±19.1 | 54.5±12.2 | **0.002** |
| **PHR** | 6554.6±1819.5 | 5765.1±1262.5 | **0.005** |
| **SYNTAX score** | 18.5±5.7 | 11.6±4.3 | **<0.001** |
| **Gensini score** | 62.3±18.5 | 39.1±10.7 | **<0.001** |
| **Single vessel disease (n, %)**<br>**Double vessel disease (n, %)**<br>**Multivessel diseases (n, %)** | 31 (31.6)<br>26 (26.5)<br>41 (41.9) | 204 (63.8)<br>66 (20.6)<br>50 (15.6) | **0.011** |
| **Chronic total occlusion (n, %)** | 32 (32.6) | 91 (28.4) | 0.078 |
| **Location of the lesions (n, %)**<br>**LMCA**<br>**LAD**<br>**Cx**<br>**RCA** | <br>26 (6.2)<br>80 (19.1)<br>64 (15.3)<br>52 (12.4) | <br>19 (4.5)<br>204 (48.8)<br>108 (25.8)<br>115 (27.5) | **0.037** |
| **Management of CAD (n, %)**<br>**PTCA**<br>**CABG**<br>**Conservative** | <br>40 (40.8)<br>46 (47.0)<br>12 (12.2) | <br>203 (63.4)<br>96 (30.0)<br>21 (6.6) | **0.008** |

**Abbreviations:** DM: diabetes mellitus; BMI: body mass index; HT: hypertension, LDL: low density lipoprotein, HDL: high density lipoprotein, TG: trygliseride; Hgb: heamoglobin; RDW: red cell distribution width; MPV: mean platelet volume; NHR: neutrophil to high density lipoprotein ratio; LHR: lymphocyte to high density lipoprotein ratio; PHR: platelet to high density lipoprotein ratio; LMCA: left main coronary artery; LAD: left anterior descending artery; Cx: circumflex artery; RCA: right coronary artery; PTCA: percutan transluminal coronary intervntion; CABG: coronary artery bypass grafting

**Table-2. Pearson correlation analysis of SYNTAX and Gensini scores with other parameters.**

| SYNTAX | | | Gensini | | |
|---|---|---|---|---|---|
| **Variables** | **r** | **p** | **Variables** | **r** | **p** |
| **NHR** | 0.314 | <0.001 | NHR | 0.307 | <0.001 |
| **LHR** | 0.196 | 0.001 | LHR | 0.174 | 0.002 |
| **PHR** | 0.286 | <0.001 | PHR | 0.264 | <0.001 |
| **Age** | 0.245 | <0.001 | Age | 0.228 | <0.001 |

| | | | | | |
|---|---|---|---|---|---|
| **BMI** | 0.240 | 0.001 | Hgb | 0.198 | 0.006 |
| **Hgb** | 0.206 | 0.004 | | | |

**Abbreviations:** NHR: neutrophil to high-density lipoprotein ratio; LHR: lymphocyte to high-density lipoprotein ratio; PHR: platelet to high-density lipoprotein ratio; BMI: body mass index; Hgb: heamoglobin

The Pearson correlation analysis revealed that NHR, LHR, PHR, age, and hemoglobin were positively correlated with both SYNTAX and Gensini scores. Body mass index was positively correlated with SYNTAX score, too. All correlated parameters, *r* and *p*-values are presented in Table-2 and figure-1.

Univariate and multivariate analyses were performed to predict DM in CAD patients. NHR, LHR, SYNTAX and Gensini scores were found to be independent predictors of DM in CAD patients (Table-3).

**Table-3. The predictors of DM in binary logistic regression analysis.**

| Variables | Unadjusted OR (95% CI) | p | Adjusted OR (95% CI) | p |
|---|---|---|---|---|
| **Age** | 1.02 (0.997-1.038) | 0.094 | 1.04 (0.982-1.126) | 0.738 |
| **BMI** | 1.07 (1.014-1.143) | 0.015 | 1.09 (0.941-1.142) | **0.008** |
| **NHR** | 1.00 (1.001-1.005) | 0.010 | 1.02 (0.999-1.162) | **0.011** |
| **LHR** | 1.01 (1.003-1.016) | 0.003 | 1.01 (1.005-1.115) | **0.038** |
| **PHR** | 1.01 (1.002-1.031) | 0.026 | 1.01 (0.986-1.026) | 0.694 |
| **Gensini** | 1.02 (1.013-1.047) | 0.001 | 1.06 (0.972-1.216) | **0.069** |
| **SYNTAX** | 1.09 (1.061-1.123) | 0.001 | 1.08 (1.031-1.134) | **0.001** |

**Abbreviations:** DM: diabetes mellitus; BMI: body mass index; NHR: neutrophil to high-density lipoprotein ratio; LHR: lymphocyte to high-density lipoprotein ratio; PHR: platelet to high-density lipoprotein ratio; OR: odds ratio; CI: confident interval

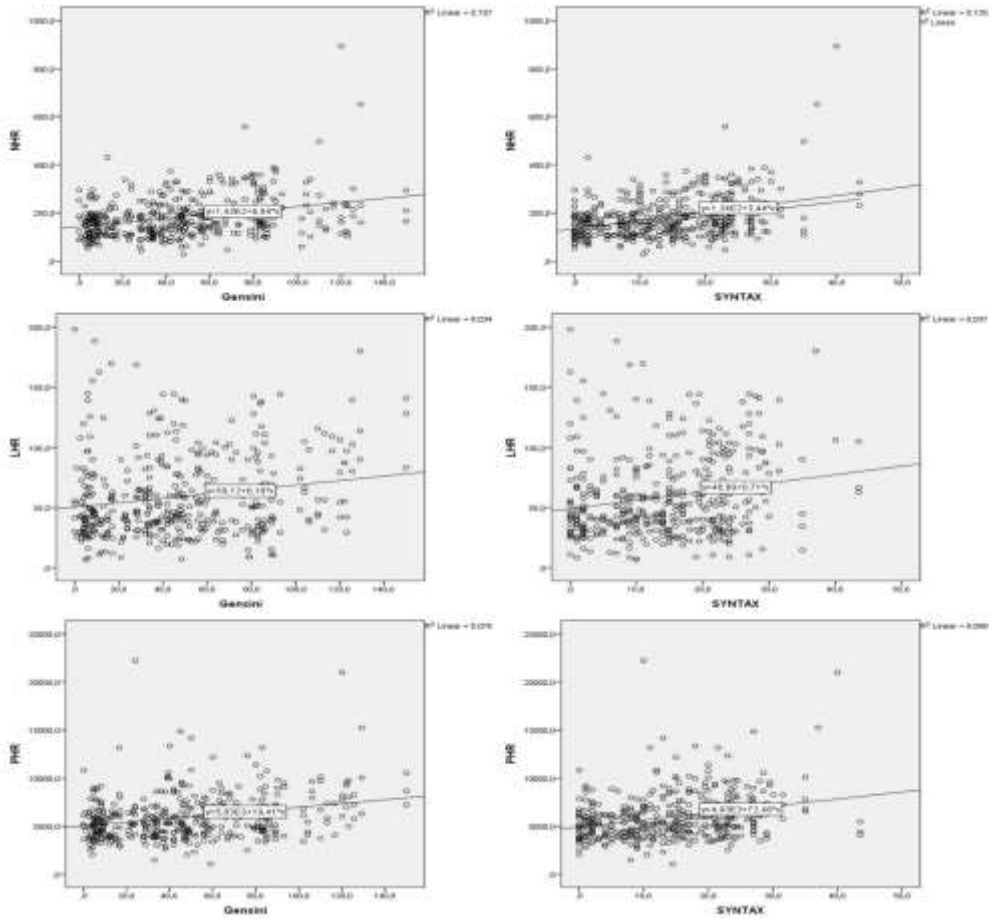


**Figure-1.** Correlation analysis showing statistically significant positive correlation between inflammatory parameters with SYNTAX and Gensini scores

## Discussion:

In this prospective study, we demonstrated that inflammatory parameters NHR, LHR, and PHR were higher in diabetic CAD patients. We also showed that SYNTAX and Gensini scores, which show the burden of atherosclerosis, are higher in diabetic CAD patients. Additionally, NHR, LHR, and PHR were positively associated with SYNTAX and Gensini scores.

Type 2 DM is a well-recognized risk factor for atherosclerosis and CAD. Type 2 DM poses a 2-fold increased risk not only for CAD but also for other vascular diseases and it is well known that cardiovascular diseases are higher in patients with DM compared with those without in the general populations (16). Several factors explain the pathophysiological connection between DM and atherosclerosis acceleration. Among these factors such as dyslipidemia with increased levels of atherogenic LDL, hyperglycemia, oxidative stress, and increased inflammation have been proposed. Chronic inflammation is a known feature that is common to both atherosclerosis and DM. Increased activity of some inflammasomes and increased levels of pro-inflammatory cytokines were demonstrated in DM patients (17). Another link between atherosclerosis and DM identified within the inflammatory pathways is neutrophil extracellular trap activation (18). Hence, studies are constantly being conducted to introduce new and reliable biomarkers for the early detection and prediction of atherosclerosis and the inflammatory link with DM disease (19, 20).

HDL prevents the accumulation of free cholesterol and triglycerides in the vessels and the formation of lipid plaques. Neutrophils, lymphocytes, and platelets, which are inflammatory immune system components, are active in blood circulation and play an important and fundamental role in inflammation through the secretion of protein substances such as cytokines (10, 21). Previous studies have investigated the relationship between neutrophil to lymphocyte ratio, monocyte to HDL ratio, NHR, PHR and coronary atherosclerosis (12, 22). Studies investigating inflammatory parameters and coronary atherosclerosis burden in diabetic and non-diabetic patients are very rare (20, 23). Based on all these, we aimed to investigate the differences in the atherosclerosis burden according to diabetic and non-diabetic patient groups who underwent coronary angiography and its relationship with NHR, LHR, and PHR.

We have demonstrated the association of NHR, LHR, and PHR with CAD severity in the context of the SYNTAX and Gensini scores. Our study revealed that MHR, LHR, and PHR are related to the SYNTAX and Gensini scores and atherosclerosis severity, so inflammation parameters were elevated in patients with stenosis in more coronary arteries.

Platelets have an important role in the etiology of the CAD and larger mean platelet volume is associated with CAD (24). In addition, HDL shows antithrombotic activity by inhibiting platelet activity (25). It has previously been stated that the platelet to lymphocyte ratio (PLR) was inversely related to HDL in CAD patients (8). In another study, PLR was associated with higher CAD severity and poor prognosis, so it can be used as a predictive biomarker of cardiovascular diseases and the risk of future events (26). Although the role of platelets in the pathogenesis of CAD is well known, the documented relationship between PHR and SYNTAX and Gensini scores in diabetic and non-diabetic patients was shown in our study for the first time. Previous studies found that neutrophil counts and neutrophil to lymphocyte ratio (NLR) were associated with the progression of atherosclerosis (27). Another study showed a positive correlation between NLR and Gensini scores, suggesting that NLR is an independent predictor of CAD severity (28). Our study also showed a significant correlation between NHR, LHR, and SYNTAX and Gensini scores in diabetic and non-diabetic patients.

### Limitations

There are some limitations in the present study that should be highlighted. Firstly, a relatively small sample size from a single center may have introduced bias. Secondly, because HbA1c levels which is an index of the fluctuation in glycaemia during 3 months were calculated at baseline, the status of glycemic control in DM patients was not fully clear. In addition, cardiovascular events and other diabetic vascular effects were not fully specified. Other limitations include that the patients with DM were older and had a higher body mass index than those without DM, although not significantly, and the rate of HT and smoking was higher in the DM group.

## Conclusion:

Our study demonstrated that NHR, LHR, and PHR were significantly and independently

associated with higher SYNTAX and Gensini scores in diabetic and nondiabetic patients. There was a deterioration in inflammatory parameters NHR, LHR, and PHR and atherosclerotic burden parameters SYNTAX and Gensini scores in diabetic patients. These inflammatory parameters might be used in daily clinical practice as a quickly accessible marker for screening CAD patients.

**Conflict of interest:** None declared

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