# Association of Diabetic Retinopathy with Angiographic Severity of Coronary Artery Disease in Patients with Non-ST Elevation Myocardial Infarction

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**Abstract:**

**Background:** Bed side ophthalmoscopic examination is a simple measure of diagnosis of diabetic retinopathy and has been shown to be a predictor of poor outcome in various cardiovascular conditions including coronary artery disease (CAD)**.** Retinopathy lesions are fairly common findings in clinic settings and may predict risk of coronary heart disease (CHD). The present study was intended to find the relationship between diabetic retinopathy with the severity of coronary artery disease in patients with NSTEMI.

**Methods:** This cross-sectional observational study was conducted in the Department of cardiology, National Institute of Cardiovascular Diseases and Hospital (NICVD), Dhaka, Bangladesh, from March 2019 to August 2020. A total of one hundred twenty DM with NSTEMI patients undergoing coronary angiogram and also fundoscopic examination with fundal photography during the index hospitalization were included in this study. Study subjects were divided into two groups on the basis of diabetic retinopathy (Group-I: NSTEMI with diabetic retinopathy ; Group- II: NSTEMI without diabetic retinopathy). Severity of coronary artery disease was determined by Gensini score and correlation between diabetic retinopathy and Gensini score was assessed.

**Results:** Gensini score was significantly higher in patients with diabetic retinopathy than that in patients without diabetic retinopathy (62.2±27.7 vs. 43.3±25.3,p<0.001).Gensini score increased with increasing severity of diabetic retinopathy(P <0.001).The risk of having severe CAD in patient with diabetic retinopathy was 13.03 (95% CI =2.410-70.419) (P<0.003).A significant correlation between diabetic retinopathy and Gensini score was noted (p value <0.001)

**Conclusion:** It may be concluded that Presence and severity of diabetic retinopathy is associated with angiographically severe coronary artery disease in patient with non-ST elevation myocardial infarction (NSTEMI) and it may be considered as an independent predictor of severity of CAD.As is a bed side assessment ,so before performing coronary angiography ,it appears to be additive for risk stratification.

**Keywords:** •Coronary artery disease •Diabetic retinopathy •Left ventricular ejection fraction •Gensini score •TVD •RCA •LCX

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## Introduction:

Cardiovascular diseases (CVDs) are the most common cause of premature death in the world. CVDs account for 50% of all non-communicable disease (NCD) deaths in the world each year and represent a significant threat to human welfare and sustainable development[1]. The exact prevalence of CAD in Bangladesh is not known. Only a limited number of small-scale epidemiological studies are available. More recent data indicates that CAD prevalence is 1.85% to 3.4% in rural population and 19.6% in an urban population[1].

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Diabetes Mellitus is a heterogeneous primary disorder of carbohydrate metabolism with absolute insulin deficiency (Type 1) or relative insulin deficiency (type 2), resistance or both leading to hyperglycemia[3]. The South Asian region shares a major proportion of this worldwide burden of diabetes. The prevalence of diabetes ranges from 0.9% in Bangladesh to 21.2% in India[4].

Diabetic retinopathy (DR) is an early and frequent marker of other vascular complications of diabetes and its relation with coronary ischemia is known[5]. Unstable angina patient with DR have more significant left ventricular dysfunction than without DR[6]. In individuals with type-2 diabetes, the presence of retinopathy signifies an increased CHD risk, independent of glycemic levels, symptomatology[7], other cardiovascular risk factors and is also associated with an increased risk of mortality and cardiovascular events[8].

While its adverse impact on vision is well known[9], the importance of retinopathy signs beyond visual impairment is less well recognized. Both non proliferative diabetic retinopathy(NPDR) and proliferative diabetic retinopathy(PDR) have now been linked with major clinical diseases like stroke, coronary heart disease, heart failure and nephropathy[10], as well as newer subclinical measure of cardiovascular disease such as coronary artery calcification and cardiac remodeling[11]. The presence of retinopathy signs has also been associated with higher degree of coronary artery calcification[12] and more diffuse/severe coronary artery stenosis on angiograms[13].

Atherosclerosis Risk in Communities study( ARIC) showed that the presence of retinopathy was associated with two-fold higher risk of incident of coronary heart disease (and myocardial infarction), three-fold higher risk of fatal coronary heart disease, and four-fold higher risk of congestive heart failure, independent of diabetes duration ,glycemic control ,smoking ,lipid profile ,and other risk factor.There is a graded ,dose dependent association of increasing diabetic retinopathy severity with increasing coronary heart disease risk[14]. The World Health Organization Multinational Study of Vascular Disease in Diabetes(WHO-MSVDD)[15] and other studies reported associations of not only NPDR but also PDR with ischemic heart disease[16].

In addition to population studies ,there are clinical studies that suggest the presence of retinopathy can be used as an indicator of silent myocardial ischemia and help guide investigative approaches in diabetic patients with suspected heart disease [17].

Coronary microcirculation dysfunction associated with diabetes, although explored extensively in recent years,[18] still represents a poorly understood phenomenon in the clinical setting. Endothelial dysfunction, with its unfavorable consequences in various vascular beds, has been widely recognized to be a result of pathophysiological processes in diabetes, with less information available in the context of the coronary microvasculature[18].

The Gensini score system is a technique developed by Gensini et al[19], for the assessment of the severity of coronary artery disease (CAD). This scoring system is based on the artery morphology, coronary anatomy, and severity of stenosis in lesions[20].

Clinicians are in constant search of a non-invasive, practical and precise tool to predict severity of coronary disease. If the association between diabetic retinopathy and the Gensini score is found, it can readily be used as a tool to predict severe CAD. The purpose of this study is to search for whether increased diabetic retinopathy is associated with increased angiographic severity in non-ST elevation myocardial infarction patients.

**Methods:**

**Study patients:**

One hundred twenty cases were selected from consecutive type 2 DM patients with NSTEMI who underwent coronary angiography between March 2019 to August 2020 and cases were divided into two groups on the basic of presence or absence of diabetic retinopathy. Type 2 DM was diagnosed according to the recommendations of the American Diabetes Association. Exclusion criteria were known duration of DM of less than 1 year, type 1 diabetes mellitus, uncontrolled hypertension (systolic blood pressure > 180 mmHg and/or diastolic blood pressure> 100 mmHg), previous coronary bypass surgery, and known nondiabetic retinal disease

**Coronary angiography:**

Selective coronary cineangiography was performed from the radial or femoral approach using Judkin's technique. Multiple views were obtained in all patients,

with the left anterior descending and left circumflex coronary arteries visualized in at least four views and the right coronary artery in at least two views by using cine-angiographic equipment. Coronary angiograms were scored according to followings-Severity score: This was the Gensini score, which has been described previously. Briefly, the coronary arterial tree was divided into segments with multiplying factors according to the functional importance of any given segment (5 for the left main trunk to 0.5 for the most distal segments) and the percent reduction in lumen diameter of each narrowing was assigned a score (0, 1, 2, 4, 8, 16, 32 according to the degree of stenosis). The sum of the scores of all segments gives the Gensini score, which places emphasis on the severity of the disease.

**Detection of Diabetic Retinopathy (DR):**

Fundoscopic examination was done one day after admission. Initially tropicamide 1.0% eye drop was given in both eyes. After full dilatation of both pupils fundoscopic examination was done by Keeller ophthalmoscope for detection of diabetic retinopathy. Then next day fundal photo was done and assessed by an ophthalmologist. Patients were divided into two groups on the basis of presence or absence of diabetic retinopathy. Those with presence of retinopathy categorized as group I and absence of retinopathy as group II.We also evaluated risk factors for CAD, which included patient age, sex, duration of diabetes, hypertension, hypercholesterolemia, smoking status, history of a cerebrovascular accident or peripheral arterial disease, and family history of CAD. Subjects who had quit smoking for over 5 years were considered non smokers.The therapeutic modality for DM (oral antidiabetics or insulin) and history of previous myocardial infarction (MI) were also recorded. Biochemical parameters including blood fasting glucose, serum total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine were noted.

**Statistics:**

Results are expressed as the mean ± SD. For univariate analysis, the significance of differences between the two groups for continuous variables was assessed with the unpaired Student's t test, while the chi-square test was used for nominal variables. Comparisons of the severity of CAD with severity of

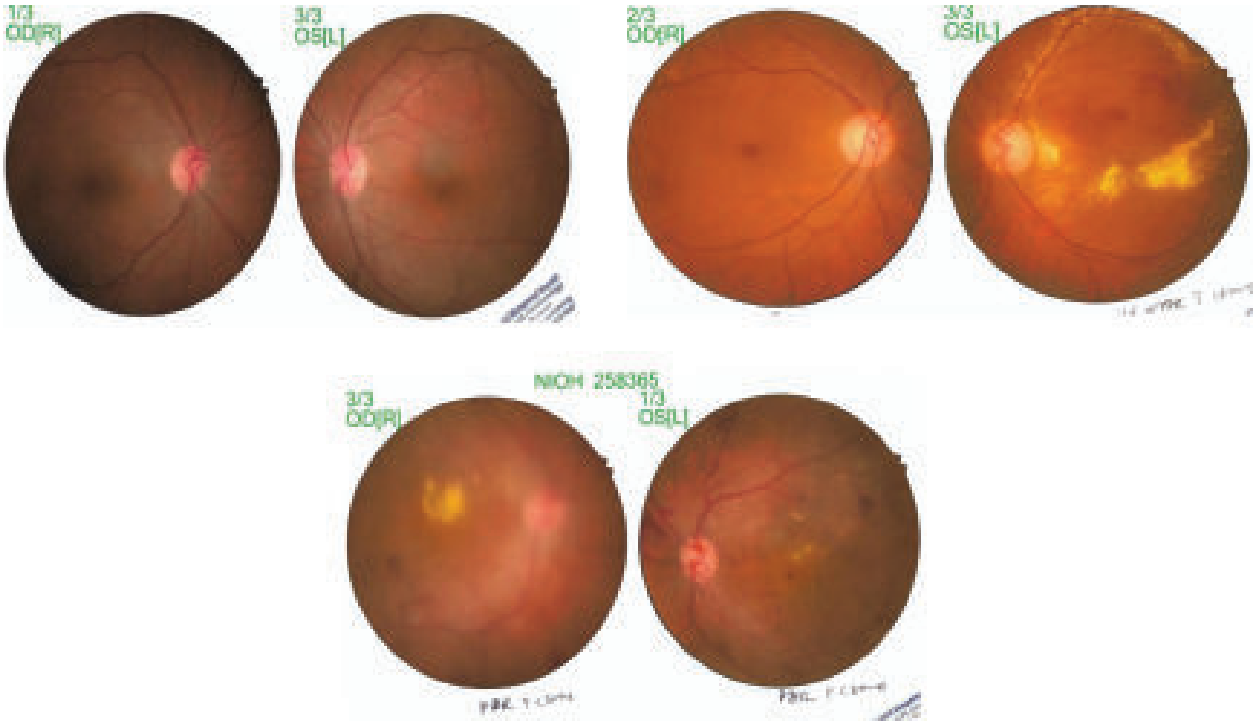


**Fig.-1:** *No diabetic retinopathy, Mild and moderate non proliferative diabetic retinopathy and Proliferative diabetic retinopathy*

diabetic retinopathy were performed with 2-way ANOVA using appropriate covariates (with parameters having significant differences in univariate analysis). The correlations between the CAD severity with other parameters were analyzed using simple correlation analysis. Multivariate associations of the CAD severity and extent scores were determined by performing multiple stepwise linear regression analysis with parameters having significant correlations in the simple correlation analysis. Statistical analyses were carried out by using SPSS 16.0 (Statistical Package for the Social Sciences by SPSS Inc., Chicago, IL, USA)

**Results:**

Diabetic retinopathy: According to the results of the fundus examinations, 60 (50%) of 120 patients had

DR (non proliferative mild in 16, moderate to severe in 22, and proliferative in 22) whereas the remaining

60 (50%) had no retinopathy.

Comparison of clinical characteristics and risk factors: The patients with DR had a significantly longer duration of known diabetes (P < 0.001), a higher ratio of being on insulin therapy (P = 0.03) in table 4.3, higher serum creatinine levels (P< 0.001 and P < 0.001, respectively).

**Table-I**

*Risk factors of the study patients (N=120).*

| Risk Factors | | Group I (n=60) | | Group II(n=60) | | p value |
|---|---|---|---|---|---|---|
| | | Number | % | Number | % | |
| Smoking | Yes | 26 | 43.3 | 31 | 51.7 | 0.36NS |
| Hypertension | Yes | 35 | 58.3 | 38 | 63.3 | 0.57NS |
| Dyslipidemia | yes | 19 | 31.7 | 14 | 23.3 | 0.31NS |
| Family H/O of premature CAD | | 13 | 21.7 | 6 | 10.0 | 0.08NS |
| Previous H/O of PAD | | 4 | 6.7 | 4 | 6.7 | 1.00NS |
| Previous H/O of CVD | | 4 | 6.7 | 3 | 5.0 | 0.69NS |
| Mean duration of DM (yrs) | | 11.8±5.7 | | 5.7±1.7 | | <0.001S |
| No. of patients taking insulin | | 22 | 36.7 | 8 | 13.3 | 0.003S |

Here,Group I=Patients with diabetic retinopathy, Group II= Patients without diabetic retinopathy p value reached from chi-square test for qualitative variables and t-test for quantitative variables. S= Significant (p >0.05)

**Table-II**

*Distribution of the study patients by biochemical status (N=120).*

| Biochemical parameters | Group I(n=60) Mean±SD | Group II (n=60) Mean±SD | p value |
|---|---|---|---|
| RBS (mmol/L) | 16.1±8.6 | 14.1±9.5 | $0.37^{NS}$ |
| Serum Creatinine (mg/dl) | 1.31±0.22 | 1.04±0.20 | $<0.001^{S}$ |
| Troponin I ng/dl | 23.39±13.92 | 21.17±12.96 | $0.37^{NS}$ |
| Total Cholesterol (mg/dl) | 204.5±18.8 | 204.3±19.7 | $0.93^{NS}$ |
| LDL Cholesterol (mg/dl) | 130.6±16.6 | 129.0±21.7 | $0.65^{NS}$ |
| HDL Cholesterol (mg/dl) | 40.1±4.7 | 39.7±5.3 | $0.74^{NS}$ |
| TG (mg/dl) | 168.8±21.4 | 172.1±29.8 | $0.49^{NS}$ |

Here, Group I=Patients with diabetic retinopathy, Group II= Patients without diabetic retinopathy RBS=Random blood sugar, LDL= Low density lipoprotein, HDL= High density lipoprotein TG= Triglycerides p value reached from unpaired t test, ns = Not significant (p>0.05), S= Significant (p<0.05)

**Table-III**

*Distribution of the study patients by Gensini score (N=120)*

| Gensini Score | Group I (n=60) | | Group II (n=60) | | p value |
|---|---|---|---|---|---|
| | Number | % | Number | % | |
| Severe CAD (>36 points) | 54 | 90.0 | 31 | 51.7 | <0.001S |
| Not severe CAD (≤36 points) | 6 | 10.0 | 29 | 48.3 | <0.001S |
| Mean ± SD | 62.2±27.7 | | 43.3±25.3 | | <0.001S |

Here,Group I=Patients with diabetic retinopathy, Group II= Patients without diabetic retinopathy S=Significant (p<0.05) CAD= Coronary artery disease
p value reached from chi square test of categorical approach and unpaired t-test of quantitative approach.

**Table-IV**

*Association between Diabetic Retinopathy and Gensini score (N=120).*

| No. of vessel involved | Gensini Score | | P value |
|---|---|---|---|
| | Mean | SD | |
| No DR (n = 60) | 43.35 | 25.30 | |
| Mild DR (n=16) | 48.69 | 19.77 | <0.001s |
| Moderate DR (n=22) | 58.27 | 23.87 | |
| Severe DR (n=22) | 75.98 | 30.86 | |

S = Significant (p<0.05),p value reached from ANOVA test.
The table shows that the patients in the DR (+) group had significantly higher Gensini scores than patients in the DR(-ve) group.

**Prediction of CAD severity:**

**Table-V**

*Univariate logistic regression for determinants of severity of coronary artery disease as assessed by Gensini score.*

| Variables of interest | Regression coefficient(β) | p value | OR | 95% CI |
|---|---|---|---|---|
| Duration of Diabetes mellitus | 0.135 | 0.02S | 1.14 | 1.025 – 1.279 |
| Insulin taking | 0.164 | 0.03S | 1.17 | 1.05 – 2.976 |
| Serum creatinine | 1.982 | 0.005S | 4.46 | 1.435 – 28.620 |
| DR (+) | 2.131 | <0.001S | 8.41 | 3.148 – 22.517 |
| Smoking | - 0.321 | 0.286 | 0.725 | 0.414 – 1.271 |
| HTN | 0.006 | 0.292 | 1.006 | 0.567- 1.784 |
| Dyslipidemia | - 0.120 | 0.703 | 0.887 | 0.478 – 1.645 |

Dependent variable: Gensini Score>36 points; Independent variables: duration of diabetes mellitus, insulin taking, serum creatinine, DR (+) ,S = Significant, NS = Not significant

The above table depicts the univariate logistic regression analysis of odds ratios for characteristics of the subjects likely to develop coronary artery disease. The variable diabetic retinopathy, duration of diabeticmellitus, creatinine were found to be significantly associated with CAD severity with their odd ratios being 8.41,1.14 and 4.6 respectively.

**Table-VI**

*Multivariate logistic regression for determinants of severity of coronary artery disease as assessed by Gensini score.*

| Variables of interest | Regression coefficient (β) | p value | OR | 95% CI |
|---|---|---|---|---|
| Duration of Diabetes mellitus | -0.125 | 0.21NS | 0.88 | 0.725 – 1.075 |
| Insulin intake | -0.480 | 0.47NS | 0.62 | 0.164 – 2.331 |
| Serum creatinine | 0.833 | 0.48NS | 2.29 | 0.219 – 24.144 |
| Presence of DR | 2.567 | 0.003S | 13.03 | 2.410 – 70.419 |

Dependent variable: Gensini score>36 points; Independent variables: duration of diabetes mellitus, insulin intake, serum creatinine, Presence of DR ,S = Significant, NS = Not significant

The above table demonstrates the multivariate logistic regression analysis of odds ratio (OR) for characteristics of the subjects likely to cause of high Gensini Score assessed as coronary artery disease severity. The variables revealed to be significantly associated with high Gensini score by multivariate analysis were entered into the model directly. The table depicts that DR (+) was found to be the significant predictor of high Gensini Score with OR being 13.03.

**Discussion:**

This study evaluated the association of diabetic retinopathy with angiographic severity of coronary artery disease in patients with Non-ST Elevation Myocardial Infarction. The mean age of the patients in group I and group II were 57.0±6.9 years vs. 56.9±6.8 years respectively. This is almost similar to the study done by Norgaz et al[6]. In this study ,male patients were 73.3% vs. 66.7% in group I and group II respectively.In the study by Norgaz et al., male patient in both the groups were 45% and 55% respectively[6]. The present study showed a smaller number of women than men in both the groups. Only 26.7% and 33.3% respectively.This gender disparity is multi factorial: less predisposition to CAD in reproductive age,overall, less health care seeking attitude of female patients and less attention by male counterparts of the family.Regarding CAD risk factors in this study, smoking, hypertension, dyslipidemia,family history of premature CAD, previous history of PAD,previous history of CAD and obesity, presented in the above table did not differ significantly between two groups. Only duration of diabetes and number of patient taking insulin were found significantly higher in group I than group II. This is almost similar to study done by Saleem et al., 2017[21].

In the present study,Gensini score of NSTEMI patients ,who underwent CAG, differed between no diabetic retinopathy ,mild diabetic retinopathy to severe diabetic retinopathy. The mean Gensini score in group I 62.2 ± 27.7 versus 43.3 ±25.3, P< 0.001.Norgaiz et al. studied the relationship between diabetic retinopathy and CAD severity by Gensini score (6). In Saleem et al 2017, it was shown that the patients with diabetic retinopathy had significantly higher vessel (2.62 ± 0.60 versus 1.9 ± 1.03, P< 0.001) and severity (103 ± 37.17.0 versus 38.55 ±22.20, P< 0.001) score than patients with no evidence of diabetic retinopathy.They demonstrated that higher the diabetic retinopathy also have severe coronary artery disease.Patient without diabetic retinopathy have mean Gensini score 43.35 ± 25.30,mild diabetic retinopathy 48.69 ± 19.77 ,moderate retinopathy score 58.27 ± 23.87 and severe diabetic retinopathy

75.98 ± 30.87 and the difference of diabetic retinopathy between the subgroups were significant. Apart from this Rong J et.al 2013., investigate association between diabetic retinopathy and CAD severity by Gensini score .They found that the prevalence of coronary atherosclerosis, is significantly higher in the patients with T2DM with DR compared with those without DR[22]. So, the overall findings relating to the association between diabetic retinopathy and CAD severity correlates with the findings of present study.In this study significant positive correlation was also found between diabetic retinopathy and Gensini score.

In the present study, univariate logistic regression analysis of the variables likely to cause severe CAD (Gensini score>36) was done.The univariate regression analysis revealed that the odds ratios of diabetic retinopathy ,duration of diabetic, number of patient

taking insulin, s.creatinine were statistically significant and independently associated with severe CAD with Gensini score >36. However, when these parameters were analyzed in multivariate logistic regression analysis, only diabetic retinopathy found to be independent determinants of severe CAD. After comparing the findings of present study with other studies,it can be summarized that there is significant correlation between diabetic retinopathy and CAD severity.

**Conclusion:**

It may be concluded that Presence and severity of diabetic retinopathy is associated with angiographically severe coronary artery disease in patient with non-ST elevation myocardial infarction (NSTEMI) and it may be considered as an independent predictor of severity of CAD.As is a bed side assessment, so before performing coronary angiography, it appears to be additive for risk stratification.

**Conflict of interest- None**

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