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Original Article

# The Coronary Artery Ectasia and Its Correlation with Matrix Metaloproteinase-9 and Reticulocyte Distribution Width in Coronary Artery Disease Patients.

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## ABSTRACT

**Background**: Although coronary artery ectasia (CAE) is thought to be a different form of vascular remodeling due to atherosclerosis, often links to endothelial inflammation and disturbance but the underlying mechanism that clearly explain this vascular abnormality is still yet unknown. Our study aimed to assess the correlation between Matrix Metaloproteinase-9 (MMP-9) levels and Reticulocyte Distribution Width (RDW) in coronary artery ectasia formation in CAD patients. **Methods**: Both basic demographic, laboratory, and angiographic data of forty-eight patients were collected and analyzed. We divided them into two groups according to coronary angiography results, where coronary artery ectasia was in the first group and obstructive coronary artery disease was in the second group. MMP-9 and RDW levels were compared between the two groups to find if there is a relationship with coronary artery ectasia. **Results**: The mean MMP-9 and RDW of the coronary artery ectasia group was higher than that of CAD group. (ROC) Curve analysis for detection of CAE cutoff regards RDW and MMP-9 in the two groups showed significant results with area under curve was 0.94, 0.97 respectively. **Conclusion**: The coronary artery ectasia was associated with the higher levels of MMP-9 and RDW. The reticulocyte distribution width (RDW) assay seems to be a simple method to predict Coronary Artery Ectasia. **Recommendations**: We see that RDW is a part of complete routine blood count which seems to be a simple, easy, inexpensive, routinely reported laboratory test may be a useful biomarker to predict coronary artery ectasia in suspected CAD patients. We need future investigation to find the effect of (RDW & MMP-9) biomarker in the prognosis and the risk stratification of patients with CAE.

**Key words**: matrix metalloproteinase-9, reticulocyte distribution width, the isolated coronary artery ectasia.

## INTRODUCTION

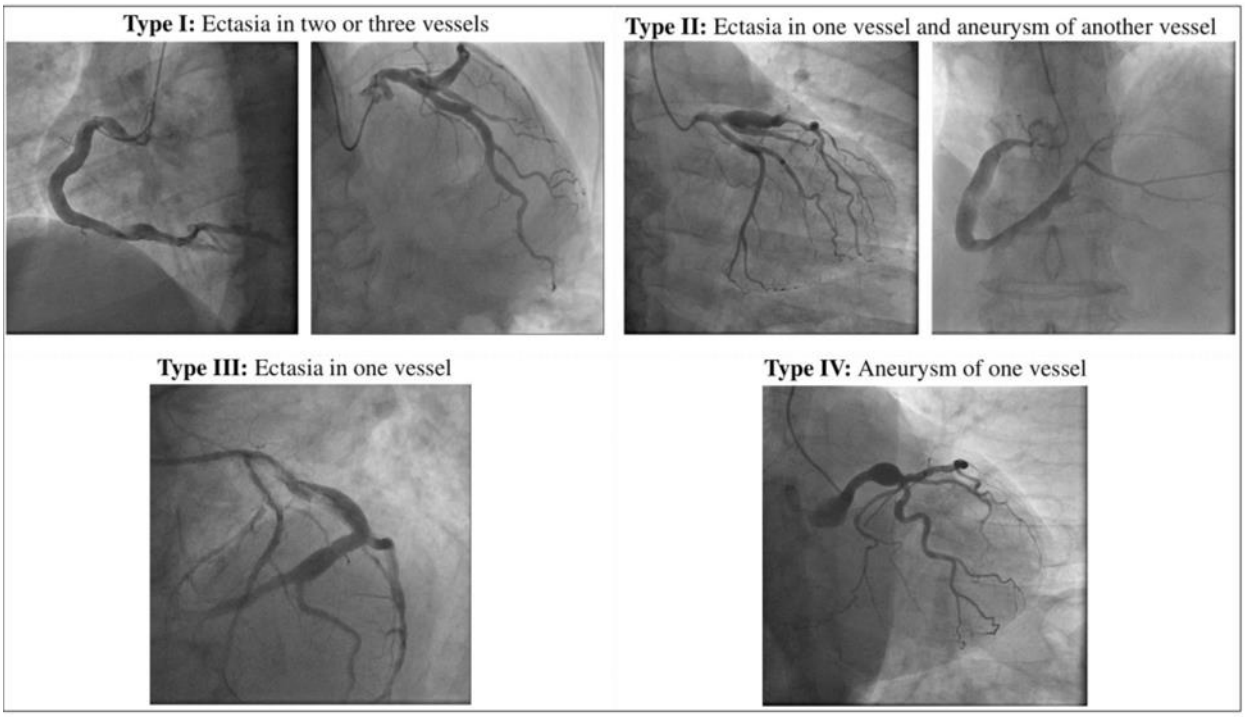
The coronary artery ectasia (CAE) is known as a dilatation that exceeds 1.5 times the normal caliber of the adjacent coronary segment. It may lead to many unfavorable events such as vasospasm, dissection, thrombosis up to acute coronary syndrome. It was found in the range of 1.2-5% in different populations [1, 2, 3, 4] Many pathologic mechanisms were involved in CAE development including chronic vascular inflammation and arterial wall stress [5]. Although CAE is thought to be a atherosclerosis vascular remodeling, the mechanism that explains the initiation of this remodeling is still controversial [6]. Recent studies found that CAE may be associated with other vessels aneurysms with common underlying pathophysiology [7]. The CAE patients have high levels of multiple inflammatory biomarkers as compared to normal coronary patients. The role of the inflammatory biomarkers in CAE pathophysiology and prognosis needs further studies [8, 9]. The Matrix MetalloProteinases (MMP) are a group of zinc-dependent extra-cellular proteolytic enzymes against collagen and elastin [10,11]. MMPs are involved in all atherosclerosis stages through inflammatory vascular endothelial dysfunction,

vascular smooth muscle cells migration (VSMC). MMP-9 participates in plaque activation, and destabilization [12]. On the other hand, many studies evaluated the importance of other inflammatory biomarkers including the reticulocyte distribution width (RDW) as a portion of the regular full blood picture; it is a measure of the size variability of circulating erythrocyte[13]. Many studies found the association of high RDW too many major cardiac events, such as acute coronary syndrome, cardiac syndrome X, myocardial reinfarction after percutaneous coronary intervention even up to slow coronary flow syndrome [14]. In contrast to the biomarkers of inflammation which are not routinely analyzed, RDW provides valuable information concerning risk stratifications in CAD patients [15]. Some studies reported that the RDW is a strong biomarker of many cardiovascular diseases and RDW has been associated with CAE [16].

## METHODS

Study population:This is a retrospective comparative study that conducted at Zagazig university hospitals (cardiology department) and included forty-eight patients with typical chest pain and a documented ischemic heart disease either by echocardiography left ventricular regional wall motion abnormality, exercise electrocardiogram or positive dobutamine stress echocardiography also must have normal hepatic and renal functions and patients who had high probability of coronary artery disease and were planned for elective coronary angiography. Patients that were documented with acute coronary syndrome, active or chronic infectious disease, documented auto-immune diseases, chronic kidney disease, history of malignancy, maintained usage of steroids, previous PCI and/or Coronary arteries bypass grafting, concomitant CAE and obstructive coronary artery disease were eliminated from this study. Persons hemolytic anemia, iron supplemental therapy that may elevate RDW levels in plasma were excluded as well. Full history taking regards gender, age, already prescribed drugs, major risking factors. Clinical examination was performed regarding general features that including patient's appearance, decubitus, complexion, temperature, blood pressure, pulse and respiratory rate. Resting twelve leads surface ECG is also recorded. Two -D transthoracic routine Echocardiography was done for all patients.

Diagnostic coronary angiography: All the coronary angiographic films were evaluated by two experts' interventional cardiologist. A conclusive review of each one of the coronary angiograms establishes the lesions site and percentage of lumen stenosis through every coronary artery lesion. Coronary artery ectasia was known as a dilatational circumference exceeds the one and half fold normal caliber in main coronary arteries. To identify the coronary artery ectasia segment, the diameter of the coronary artery was calculated and calibrated with the catheter diameter, by using automatic coronary analysis software (Siemens & GE). The types of coronary artery ectasia were classified according to Markis et al.; Type I, diffuse CAE in 2 or 3 coronary vessels; Type II, diffuse CAE in one coronary vessel and localized disease in another one; Type III, diffuse CAE in a single vessel; and Type IV, segmental localized CAE (figure 1),[17 &18]. Obstructive CAD is known as any circumstantial narrowing more than fifty percent in any major coronary artery [(LM), (LAD), (LCX)&(RCA)]. According to the coronary angiography results, the forty-eight patients were categorized into two groups. The first group consisted of twenty-four patients with obstructive coronary artery disease (CAD group). The second group consisted of twenty-four patients with coronary artery ectasia (CAE group).




**(Figure 1):** The coronary artery ectasia; Markis classifications:( Quoted: from: Esposito et al.,) [18]

Laboratory investigations:

The human (MMP-9) assay was measured in Heparin plasma using (Quantikine, Human MMP-9 Assay) (R&D Systems Europe Ltd, UK). The total assay was a quantitative detection of MMP9 in serum by using Human MMP9 ELISA Kit with a monoclonal antibody specific for MMP9 pre-coated onto the wells. Blood samples were drained into EDTA containing tubes after a period of 8 hours fasting from ante-cubital vein. Serum separation was done by centrifugation for ten minutes then stored at -20ºC. The frozen samples were collected and sent to the central hospital laboratory. RDW is determined by an automated blood counter (SYSMEX XT-1800i counter) used for whole blood analysis. All routine lab assessments were done for all patients including one of inflammatory markers (serum highly sensitive CRP). All measures were done at our hospital`s central Laboratory.

**Statistical analysis**

The data collection according to history taking, demographic, and laboratory results were analyzed using Microsoft Excel & SPSS version 20 software. The statistical tests and parameters that were used: Mean standard deviations, the student t-test, and the chi square (X2) test. P value was set at <0.05 to have a significant result and <0.001 for higher significant results. The Receiver Operator Characteristic curve (ROC) analysis was carried out for detection of CAE and found the best cutoff regards RDW and MMP-9 and calculation of the sensitivity, the specificity, and the area under the curve (AUC).

## RESULTS

A total of twenty-four patients with CAE; males represented (87.5 %) with mean age (58.8±11) and twenty-four patients with obstructive CAD; males represented (66.7%) with mean age (54.7±6.1) were selected in our study. The two groups were comparable regarding age, gender, and smoking. There was no statistically significant difference between the study groups regarding basic data (table 1). Regarding risk factors distribution such as Diabetes mellitus (DM), hypertension and dyslipidemia; it was found that DM is significantly associated with CAD group (79.2%) than that CAE group (20.8%). As for dyslipidemia it was insignificantly associated with CAD group (54.2%) over CAE group (29.2%). And for hypertension there was not any statistically significant difference among the studied groups (CAD 87.5%, CAE 70.8%) (Table 1). As for echocardiographic resting left ventricular wall motion abnormality there was no statistically significant difference among the two groups as the obstructive CAD group had

echocardiography LV RWMA in 90 % of the cases and CAE group had echocardiography LV RWMA in 87.5% of the cases (Table 1). Both studied groups also were comparable regarding mean serum highly sensitive CRP levels as there was no statistically significant difference between the CAD group (1.30±0.65) and the CAE group (1.65±1.03) (P value <0.1659) (table1). The Coronary artery ectasia (CAE) group was significantly higher regards reticulocytes distribution width (RDW) (15.5±1.8) and Matrix metalloproteinase-9 (MMP-9) (5.4±4.8) than the obstructive coronary artery disease (CAD) group (RDW 12.19±1.04) and (MMP-9) (1.02±0.6) (P value <0.00) (Table 1) (figure 2,3). According to the ROC curve analysis, RDW >16.45% was the optimal cutoff value for detection of CAE According to the ROC curve analysis, RDW >16.45% was the optimal cutoff value for detection of CAE with a sensitivity of 91.7% & a specificity of 90.2% (P < 0.001). According to the ROC curve analysis, the human MMP-9 >5.6 ng/ml was the optimal cutoff value for detection of CAE with area under curve = 0.976 with a sensitivity of 95.8% & a specificity of 91.5% (95% CI 0.939, 1.000; P < 0.001) (Table 2) (figure 4). There was a statistically significant association and agreement between cut-off and CAE (Kappa agreement for RDW and MMP-9 is 0.84 and 0.83 respectively) (P value <0.001) (table3). According to angiographic data; the frequency of coronary involvement, in CAE group : (LAD) was16.6%, (RCA) was 50 %, (LCX) was 33.33% .By using the Markis classification of coronary ectasia, type I ectasia was most common (50%), followed by type III (33.33%) then type II (8.3%) and type IV (8.3%), (Table 4).

**Table (1):** Baseline demographic, clinical, and echocardiographic & laboratory data of the studied groups

| Data | | | CAD group ( n=24) | CAE group (n=24) | Total | T X2 | P value |
|---|---|---|---|---|---|---|---|
| Age (year) (M±SD) | | | 54.79±6.12 | 58.87±11.0 | | T=-1.589 | 0.119 |
| Gender | Female | N | 8 | 3 | 11 | X2=2.94 | 0.086 |
| | | % | 33.3% | 12.5% | 22.9% | | |
| | Male | N | 16 | 21 | 37 | | |
| | | % | 66.7% | 87.5% | 77.1% | | |
| Smoking | No | N | 11 | 8 | 19 | $X^{2=}$0.78 | 0.37 |
| | | % | 45.8% | 33.3% | 39.6% | | |
| | Yes | N | 13 | 16 | 29 | | |
| | | % | 54.2% | 66.7% | 60.4% | | |
| DM | No | N | 5 | 19 | 24 | X2=16.33 | 0.00** |
| | | % | 20.8% | 79.2% | 50.0% | | |
| | Yes | N | 19 | 5 | 24 | | |
| | | % | 79.2% | 20.8% | 50.0% | | |
| HTN | No | N | 3 | 7 | 10 | X2= 2.02 | 0.15 |
| | | % | 12.5% | 29.2% | 20.8% | | |
| | Yes | N | 21 | 17 | 38 | | |
| | | % | 87.5% | 70.8% | 79.2% | | |
| Dyslipidemia | No | N | 11 | 17 | 28 | X2=3.08 | 0.079 |
| | | % | 45.8% | 70.8% | 58.3% | | |
| | Yes | N | 13 | 7 | 20 | | |
| | | % | 54.2% | 29.2% | 41.7% | | |
| Echo RWMA | -VE | N | 3 | 3 | 6 | $X^{2=}$3.2 | 0.174 |
| | | % | 12.5 % | 12.5% | 12.5% | | |
| | +VE | N | 21 | 21 | 42 | | |
| | | % | 87.5% | 87.5% | 87.5% | | |
| RDW % (M±SD) | | | 12.19±1.04 | 15.5±1.8 | | T=-7.768 | 0.00** |

| Data | CAD group ( n=24) | CAE group (n=24) | Total | T X2 | P value |
|---|---|---|---|---|---|
| MMP-9 (ng/ml)(M±SD) | 1.02±0.6 | 5.48±4.82 | | T=-4.493 | 0.00** |
| Hs- CRP mg/dl (M±SD) | 1.30±0.65 | 1.65±1.03 | | T=1.4078 | 0.1659 |

T: Independent samples of the Student's t-test
$X^2$ : Chi-square test .
p< 0.05 is significant. **p<0.01 is highly significant

**Table 2:** the cutoff value of RDW & MMP-9 in detection of CAE

| Test Result Variable(s) | Cutoff | Sensitivity | Specificity | Area under the curve | P | 95% Confidence Interval | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower Bound | Upper Bound |
| RDW (%) | > 16.45 | 91.7% | 90.2% | 0.943 | 0.00** | 0.874 | 1.000 |
| MMP_9(ng/ml) | > 5.6 | 95.8% | 91.5% | 0.976 | 0.00** | 0.939 | 1.000 |

**Table 3:** Association and agreement between cutoffs in the studied group

| | | | Group | | Total | $X^2$ | P | Kappa agreement |
|---|---|---|---|---|---|---|---|---|
| | | | CAD | CAE | | | | |
| RDW | < 16.45 | N | 22 | 2 | 24 | 33.83 | 0.00** | 0.84 |
| | | % | 91.7% | 8.3% | 50.0% | | | |
| | > 16.45 | N | 2 | 22 | 24 | | | |
| | | % | 8.3% | 91.7% | 50.0% | | | |
| MMP-9 | < 5.6 | N | 21 | 1 | 22 | 33.61 | 0.00** | 0.83 |
| | | % | 87.5% | 4.2% | 45.8% | | | |
| | > 5.6 | N | 3 | 23 | 26 | | | |
| | | % | 12.5% | 95.8% | 54.2% | | | |

**Table (4):** number & frequency of coronary artery vessel & grades of ectasia according to Markis classifications

| Angiographic data | CAD group | | CAE group | |
|---|---|---|---|---|
| | N | % | N | % |
| LM (N & %) | 1 | 2 | 0 | 0 |
| LAD | 19 | 39.58 | 8 | 16.66 |
| LCX | 18 | 37.5 | 16 | 33.33 |
| RCA | 10 | 20.83 | 24 | 50 |
| type I ectasia | | | 12 | 50 |
| type II ectasia | | | 2 | 8.3 |
| type III ectasia | | | 8 | 33.33 |
| type IV ectasia | | | 2 | 8.3 |

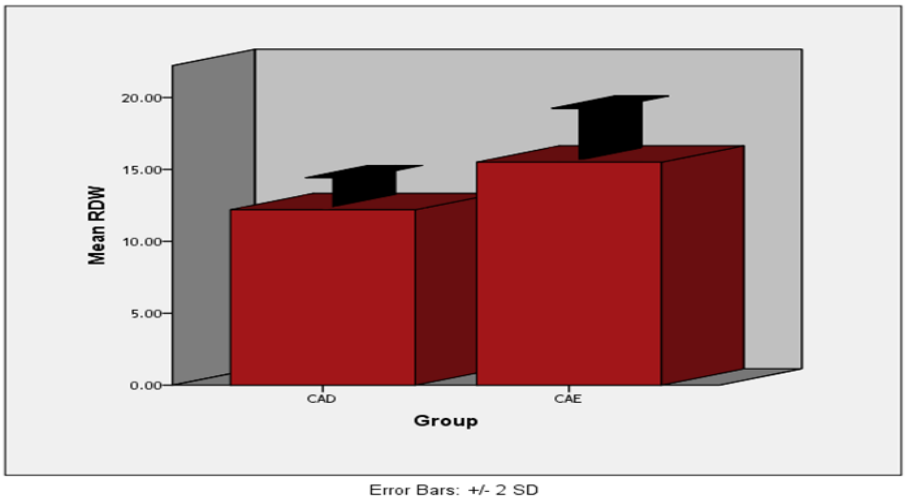



**Figure 2:** CAE group is significantly higher as regards RDW

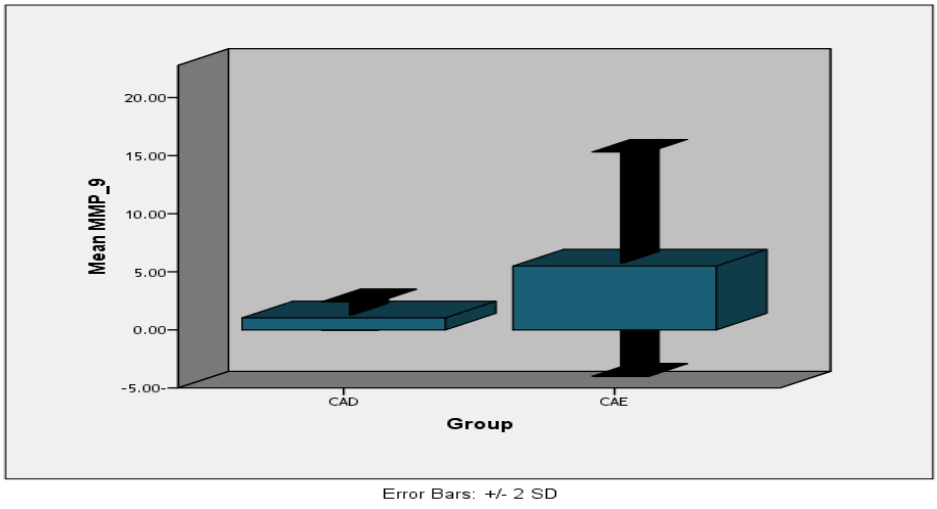



**Figure 3:** CAE group is significantly higher regard MMP-9

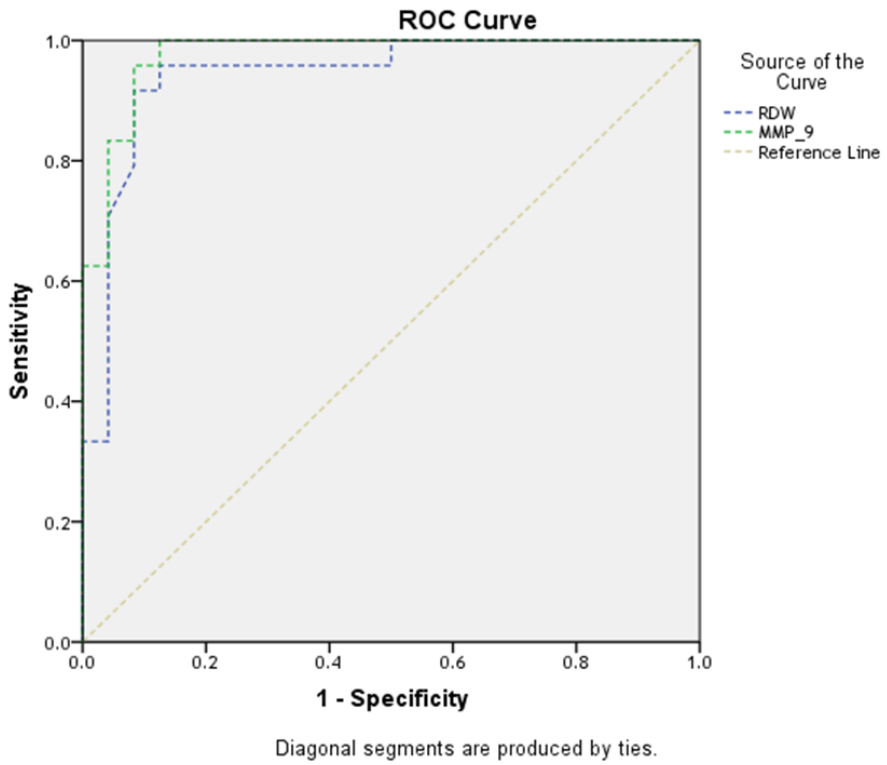



**Figure 4**: the ROC curve analysis Receiver operating characteristic (ROC) Curve for detection of CAE cutoff regards MMP-9 & RDW**.**

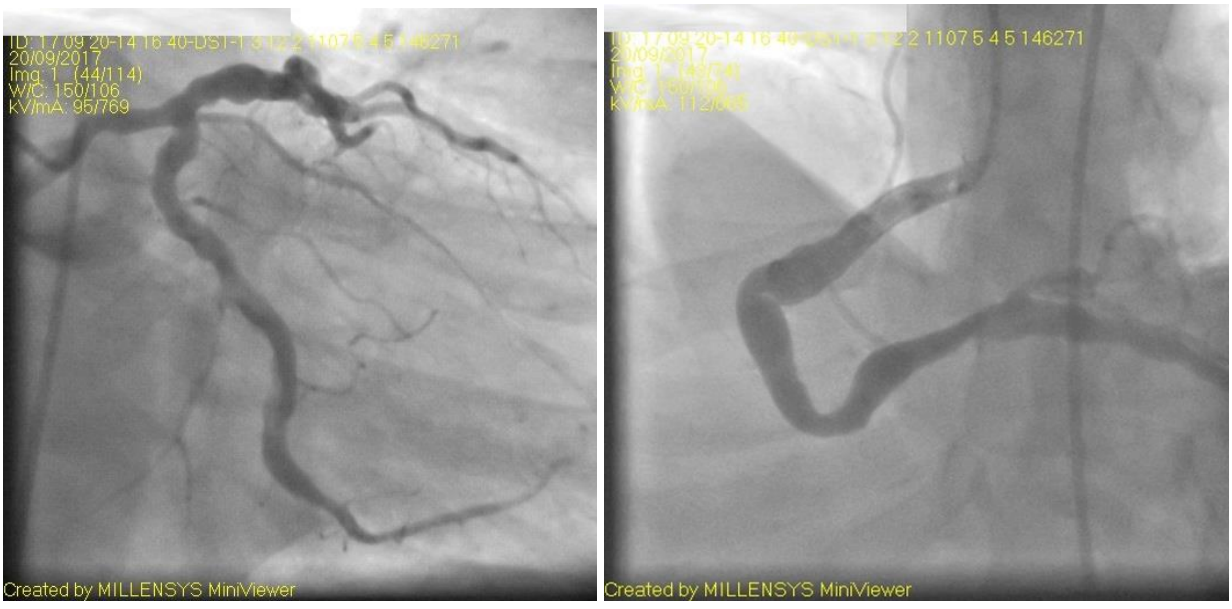



**Figure 5:** case demonstrations of CAE group: (type I ectasia) markis classifications

## DISCUSSION

The angiographic definition of CAE is a dilatation that exceeds 1.5 times the normal caliber of the adjacent normal coronary segment [1]. The real causing mechanisms of abnormal dilatation in CAE are still unknown, but many studies were suggesting genetic predisposition, combining risk factors for atherosclerosis and abnormal inflammatory process in the vessel wall [2,19]. This retrospective comparative study involved forty-eight patients to assess the correlation between Matrix metallo-proteinase-9 levels and Reticulocyte Distribution Width (RDW) in coronary artery ectasia (CAE) group and CAD group. The present results demonstrated that MMP9 & RDW values were statistically significantly higher in patients with CAE than CAD patients. The results of our study were consistent with the risk factors distribution in the groups of Daoud et al., as there was no statistically significant difference between the study groups regarding age, gender, and smoking [20]. These results also agreed with Yalcin et al. that also showed similar results regarding age, sex, and smoking [21]. According to the clinical risk factors as hypertension, dyslipidemia, and diabetes mellitus there was no statistically significant difference between the studied groups for hypertension and dyslipidemia, on the other hand diabetes mellitus was significantly associated with the coronary artery disease (CAD) group than the Coronary Artery ectasia (CAE) group. These results were concordant with Li X-L et al., and Keser et al., as there was no difference among the studied groups according to hypertension and dyslipidemia also for diabetes mellitus it was associated more with the CAD and normal group than the CAE group (22,23). Huang et al., stated that the incidence of DM in CAE patients was 8% to 33% and was 13.5% to 35% in non CAE patients .a reduced rate of DM in CAE compared to patients without CAE ($p<0.0001$) [41] In the present study, the echocardiography two-dimensional regional wall motion abnormalities of the left ventricle in (CAD) group was not statistically significant higher than in (CAE) group. This was agreed with Saglam et al., who discussed a similar study which included ninety patients proven that CAE was no statistically significant than CAD regarding left ventricular wall motion abnormality [24]. RDW is a measure of the RBCs size variability. Elevated RDW, is known as anisocytosis, that is caused by erythrocyte maturation disturbance. A chronic inflammatory state may lead to immature RBCs to enter the circulation, resulting in elevated RDW(26). In our study CAE group was significantly higher regards RDW compared to CAD group. The results of our study were comparable with Keser et al. study where 306 patients who underwent coronary angiography where 126 patients were selected to have CAE, 104 patients randomly selected to have CAD and 76 patients were selected to have normal coronary angiography. Patients with type I CAE had higher RDW values ($19.48 \pm 11.81$) than CAD ($15.54 \pm 7.87$) group and the control ($13.59 \pm 5.78$) group ($p < 0.05$) (23).On the other side, Li, X.-L., et al., questioned the correlation of RDW with CAE where 414 study population included one hundred and thirteen patients with only isolated CAE (group I) and one hundred and forty four patients known with CAD (group II) and one hundred and fifty seven patients underwent coronary angiography and had normal coronaries (group 3) who underwent coronary angiography. The levels of RDW were significantly higher in group A (CAE) ($12.97 \pm 1.4$) and B (CAD) ($12.88 \pm 1.0$) compared with that in group C (normal CAG) ($12.34 \pm 0.9$), p value = 0.020) while no difference was found between CAE ($12.97 \pm 2.4$) vs. CAD ($12.88 \pm 2.0$), p value = 0.17) (22). Dogdu et al., reported that fifty-four patients with CAE was compared to forty normal individuals with the following results: RDW were higher in the CAE group as compared with the normal individuals that RDW may be a useful biomarker for the presence of isolated CAE [25]. In another study, the RDW values ($16.88 \pm 9.40$) in CAE group were higher than CAD group ($15.54 \pm 7.87$) than in the control normal group ($13.59 \pm 5.78$) (p value < 0.05). However, no significant difference between the CAE group and CAD group was observed [23]. This discordant with our results may be due to the small sample size in our study. Our study results of MMP-9 were significantly higher in group of CAE patients ($5.48 \pm 4.82$) in comparison to obstructive CAD patients

(1.02±0.6). Our results were agreed with the result of Dogan et al., as they studied MMP3, MMP9, and TIMP1in 28 CAE patients, 27 CAD patients, and 22 normal control patients (normal coronary angiography). MMP9 levels were elevated in CAE group in comparison with obstructive CAD and normal control groups raising high hopes for suggestions about severe inflammation could be implicated in the pathogenesis of coronary artery ectasia (CAE) [27]. Ammar, W., et al., also agreed with our results in their study that had 30 patients with isolated CAE, 30 patients with obstructive CAD and 20 patients with normal coronary angiography. MMP-9 plasma levels were significantly elevated in CAE and CAD patients than with the normal control patients. MMP-9 levels were elevated in CAE group more with multivessel CAE than with CAD and control group. MMP9 plasma levels were elevated in CAE group with 70% specificity and 73.3% sensitivity (AUC=0.78, P = 0.001)[28]. Keser et al. stated that inflammation was among the contributing pathophysiology of CAE. Konstantino et al. talked out the important role of MMP9 in the development and destabilization of the plaque and pointed out that Matrix metalloproteinase-9 (MMP9) may play a role as a biomarker for (ACS) [29]. Extracellular matrix degradation by MMPs might exhaust the vessel wall connective tissue, therefore leading to weakening and dilatation of the vessel wall. MMP9 dissolves gelatin and collagens [30]. Blankenberg et al., found that there was a high relationship between high human MMP-9 levels and unfavorable cardiac outcomes [31]. Similar studies found that higher levels of MMP-9 and MMP-3 were associated with coronary artery ectasia and were correlated with its severity. The underlying pathophysiology could be extracellular matrix and connective tissue degradation [32,33]. In our study, CAE was seen in the RCA more than LAD & LCX. This was concordant with many studies, that the RCA was the most common coronary artery for CAE that was followed by LAD, LCX and LM [34,35]. In our study Type I coronary artery ectasia was seen most. Similar studies showed type I CAE and type III coronary artery ectasia were seen most [36]. In contrast to our results; It was found that, hs-CRP levels were elevated in CAE patients than CAD patients and it was explained by an active continuous inflammatory process in CAE patients [37,38,39,40].

**Study limitations**: The small sample size of the study in a single center could limit the strength of results and conclusions. The unavailability of (intravascular ultrasound) IVUS and established inflammatory biomarkers, such as MMP2, interleukin 6, is another limitation of the present study. There was no follow up for serial MMP-9 and RDW levels to see if there are changes in these results with changes in CAE.

## CONCLUSION

Coronary artery ectasia was associated with the higher levels of MMP-9 and RDW. The reticulocyte distribution width (RDW) assay seems to be a simple method to predict Coronary Artery Ectasia.

## RECOMMENDATIONS

We see that RDW is a part of complete routine blood count which seems to be a simple, easy, inexpensive, routinely reported laboratory test may be a useful biomarker to predict coronary artery ectasia in suspected CAD patients. We need future investigation to find the effect of (RDW & MMP-9) biomarker in the prognosis and the risk stratification of patients with CAE.

**Future directions**: There are many further investigations to be assessed before the human MMP-9 to be used as a documented diagnostic and prognostic biomarker.

**Conflict of interest**: No conflict of interest to be cleared.

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