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## Relation of Red Cell Distribution Width with Thromboembolic Risk in Patients Had Non-valvular Atrial Fibrillation.

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**ABSTRACT**

Higher red blood cell distribution width (RDW) anticipates harmful events among patients have cardio-vascular diseases. On other hand, there is imperfect information concerning the association between RDW and thrombo-embolism hazard in the patients with atrial fibrillation. We intended to study the relation between RDW and CHA2DS2-VASc scores which utilized for assessment of thrombo-embolic hazard in patients with non- valvular AF. Our study enrolled 46 patients with AF. We calculated CHA2DS2-VASc score for every patient, and we investigate the laboratory and echocardiographic parameters. Depend on CHA2DS2-VASc scores; we classified the AF patients into two groups (low - intermediate risk and high risk groups). Then, we compared mentioned parameters between the 2 groups, and we assessed the relation between RDW and CHA2DS2-VASc score. Multivariate regression analysis was done to find independent predictors of high CHA2DS2-VASc scores. Patients with elevated CHA2DS2-VASc scores had older age and higher RDW, hs-CRP, creatinine serum level, left atrial diameter and intervetricular septum thickness comparably to low CHA2DS2-VASc score group. Multivariate regression analysis appeared that RDW and hs-CRP were independent predictors for high CHA2DS2-VASc scores. RDW is significantly associated with CHA2DS2-VASc score among patients have AF. Furthermore, RDW considers an independent predictor in CHA2DS2-VASc score**.**
**Keyword:** non-valvular atrial fibrillation, thrombo-embolism, CHA2DS2-VASc

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## INTRODUCTION

Risk of incidence of cerebrovascular stroke and thrombo-embolism is incremented among patients have AF, which is considered the most common type of cardiac arrhythmia [1].nowadays, CHA2DS2-VASc score is suggested for assessment thromboembolic risk among patients have non-valvular AF [1]. (RDW) defined as a quantum measure of size variability of circulating RBCs that may indicates inflammation and oxidative stress status. Lately, numerous studies have revealed that elevated RDW values predict adverse events among patients with heart failure, acute coronary syndrome and cerebrovascular ischemic stroke. Studies [2]-[4] on the relation between RDW and thrombo-embolic risk in AF are scantly. Our goal was to detect the relation between RDW and CHA2DS2-VASc scores which utilized for the assessment of thrombo-embolic risk among patients have AF.

## METHODS

### Study population

A total of 46 successional patients who employed in our study between July 2017 and December 2017. Non-valvular atrial fibrillation defined as the absence of rheumatic mitral valve stenosis (more than mild mitral stenosis) and prosthetic heart valve in patient with atrial fibrillation. Inclusion criteria were at least one bout of symptomatic atrial fibrillation within the previous six months recorded by 12-lead electrocardiogram (ECG) [5]. Patients with heart failure, mitral valve stenosis (more than mild MS), prosthetic heart valve, congenital heart disease, hypothyroidism, hyperthyroidism , anemia, malignancy, renal, hepatic impairment and  acute or chronic inflammatory diseases were excepted from the study.in addition; patients who had a recent history (during preceding one month) of blood transfusion were also excluded.

### Study protocol

In our study, we utilized CHA2DS2-VASc score for evaluate the risk of thrombo-embolism in patient non- valvular atrial fibrillation (Table 1). Therefore, a score of < 2 was considered as low-intermediate risk and ≥2 was considered high risk. Full history taking , complete physical examination , laboratory examination ( CBC, creatinine , Na ,K, hs-CRP ) and  cardiac investigations (  12-lead ECG , transthoracic echocardiography ) were done on all patients. Every patient had at least one (12-lead ECG strip) revealed atrial fibrillation. **(Table 1)**

**Table (1): CHA$_2$DS$_2$-VASc score:**

| Risk factor | Score |
|---|---|
| Congestive heart failure / LV dysfunction | 1 |
| Hypertension | 1 |
| age≥75 | 2 |
| Diabetes mellitus | 1 |
| Previous stroke/TIA/thromboembolism | 2 |
| Vascular disease | 1 |
| Age 65-74 | 1 |
| Sex female | 1 |

Abbreviations: LV, left ventricle; TIA, transient ischemic attack.

Complete blood count (CBC) testing was available using standard methods providing data on total lecuocytic count (TLC), hemoglobin (Hb) levels, platelets count and RDW on admission. RDW was calculated as the width of the RBC distribution curve at a relative height of 20% above the baseline by automatic blood count instrument measured in N100.000 RBC volume using an automated assay on samples obtained for standard of caring Assessment. Serum creatinine (Cr), serum potassium (K) and serum sodium (Na) were measured after fasting for twelve hours (12 hr) a (Bekman AU 480) analyzer. hs-CRP measurements were conducted by a (Response 910) analyzer (Diasys, Germany) using the turbi-dimetric method.

A transthoracic echocardiographic examination was done in all patients via the Vivid-6 system equipped with a 2.2 MHz transducer according to recent guidelines of The European Association of Cardiovascular Imaging [6]. Left atrial diameters (LAD), interventricular septal thickness (IVST), left-ventricular end-diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD) and left ventricular ejection-fraction (LVEF) were assessed. The Local Ethics Committee approved the study protocol while written informed consent was obtained from all patient.

**Statistical analysis**

Quantities variables were expressed as mean ± standard deviation, whereas qualitative variables were expressed as one hundredth values. Comparisons between the two groups were done via the Student t test or Mann-Whitney U test or chi-square tests. Multiple regression analysis done to detect the independent predictors of high CHA2DS2-VASc score. Receiver operating curve (ROC) analyses were utilized to identify the cut-off value of (RDW) in prediction of CHA2DS2-VASc score. Correlation analyses between variables were done via Pearson or Spearman correlation. A P- value of <.05 was considered significant. All statistical analysis was done via -SPSS 17.0.

## RESULTS

The mean age of (46) patients employed in this study was (55.33±12.32) years, and 56.5% of the included study population was female. High -CHA2DS2-VASc score group had higher (RDW) values, higher serum creatinine, higher hs-CRP, higher left atrium diameter and higher interventricular septum thickness versus to the low-intermediate CHA2DS2-VASc score group **(Table 2).**

**Table (2): clinical, laboratory and echocardiographic characters depend on patients who have non-valvular atrial fibrillation.**

| item | Low-intermediate risk (n =23) | High risk (n =23) | p-value |
|---|---|---|---|
| Sex(female) | 12 (52.2%) | 14 (60.9%) | 0.552 |
| Age | 46.96 ± 10.42 | 63.70 ± 7.46 | 0.000 |
| Hypertension | 2 (8.7%) | 16 (69.6%) | 0.000 |
| Diabetes mellitus | 1 (4.3%) | 19 (82.6%) | 0.000 |
| Previous stroke | 0 (0.0%) | 11 (47.8%) | 0.000 |
| Peripheral vascular dis. | 0 (0.0%) | 7 (30.4%) | 0.000 |
| Lone AF | 17 (73.9%) | 0 (0.0%) | 0.000 |
| LAD(cm) | 3.85 ± 0.37 | 4.93 ± 0.84 | 0.000 |
| LVEF (%) | 63.39 ± 8.37 | 63.38 ± 9.86 | 0.997 |
| IVST(cm) | 0.99 ± 0.14 | 1.22 ± 0.26 | 0.027 |
| LVEDD(cm) | 4.95 ± 0.55 | 5.00 ± 0.92 | 0.799 |
| Createnine(mg/dl) | 0.81 ± 0.24 | 1.17 ± 0.23 | 0.030 |
| Na(mmol/l) | 139.61 ± 4.58 | 140.70 ± 4.88 | 0.440 |
| K (mmol/l) | 4.03 ± 0.41 | 4.00 ± 0.36 | 0.821 |
| TLC(x$10^9$) | 8.17 ± 1.43 | 8.86 ± 1.53 | 0.123 |
| Hb(gm/dl) | 14.27 ± 1.45 | 13.83 ± 1.07 | 0.249 |
| RDW (cv %) | 12.34 ± 0.56 | 14.47 ± 0.59 | 0.000 |
| Platelets (x$10^9$) | 184.83 ± 68.16 | 226.57 ± 81.90 | 0.067 |
| hs-CRP(mg/dl) | 2.60 ± 1.8 | 9.99 ± 2.32 | 0.000 |

Abbreviations: (LAD), left atrial diameter; (IVST), inter-ventricular septal thickness; (LVEDD), left ventricular end-diastolic diameter ;( LVEF), Left ventricular ejection fraction; (TLC), total leucocytic count ; (Hb), hemoglobin; (RDW), red blood cell distribution width; (K), potassium; (Na), sodium;( hs-CRP), high sensitive c reactive protein

According to the correlation analysis CHA2DS2-VASc score showed significant relationships with RDW ( r = 0.892 / p value 0.000 ), LA Diameter (r = 0.818/ p value 0.000) , IVST ( r = 0.488 p value 0.001), serum

creatinine ( r = 0.648 / p value 0.021) , platelets count ( r = 0.294 / p value 0.04 ) and hs-CRP ( r = 0918 / p value 0.000).**(Table 3 )**

**Table (3): Correlation between CHAD2VASC2 score and all parameters of studied patients**

| Parameters | CHAD2VASC2 SCORE | |
|---|---|---|
| | R | P-value |
| Age (years) | 0.704** | 0.000 |
| LAD(cm) | 0.818** | 0.000 |
| LVEF (%) | -0.180 | 0.233 |
| IVST(cm) | 0.488** | 0.001 |
| LVEDD(cm) | 0.024 | 0.874 |
| creatinine(mg/dl) | 0.648** | 0.021 |
| Na(mmol/l) | 0.105 | 0.489 |
| K(mmol/l) | -0.013 | 0.929 |
| TLC(x10⁹/l) | 0.380** | 0.119 |
| HB(gm/dl) | -0.123 | 0.414 |
| RDW (cv %) | 0.892** | 0.000 |
| platelets(x10⁹/l) | 0.294* | 0.048 |
| hs-CRP(mg/dl) | 0.918** | 0.000 |

Abbreviations: (LAD), left atrial diameter; (IVST), inter-ventricular septal thickness; (LVEDD), left ventricular end-diastolic diameter ;( LVEF), Left ventricular ejection fraction; (TLC), total leucocytic count ; (Hb), hemoglobin; (RDW), red blood cell distribution width; (K), potassium; (Na), sodium;( hs-CRP), high sensitive c reactive protein

Multi-variate regression analysis was done to predict high CHA2DS2-VASc scores revealed that RDW and hs-CRP were the most significant independent variable to predict thromboembolic risk in non valvular atrial fibrillation**. (Table 4)**

**Table (4): Multivariate regression analysis to detect the independent variables to predict high CHAD2VASC2 score**

| Variable | B | OR | P-VALUE |
|---|---|---|---|
| RDW | 5.146 | 171.752 | 0.002 |
| Creatinine | 1.450 | 4.262 | 0.237 |
| LAD | 2.271 | 4.688 | 0.120 |
| hs-CRP | 3.472 | 32.197 | 0.017 |

The best cut-off value of (RDW) to predict high CHA2DS2-VASc score was 13.4%. A RDW value higher than 13.4% has a sensitivity of (84.1%) and a specificity of (90%). (Figure 1
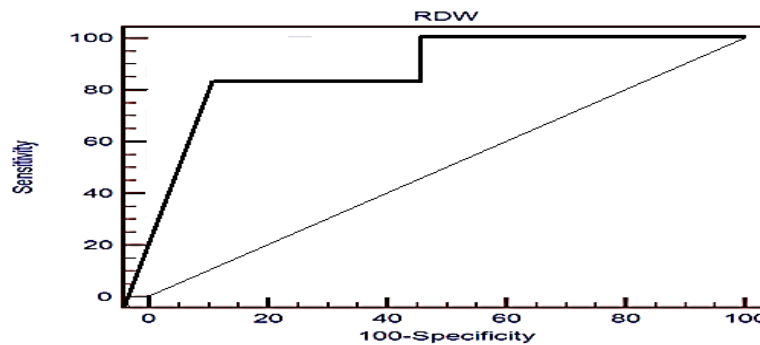
**Figure (1): ROC curve for RDW to predict CHAD2VASC2 score. ≥ 2**

## DISCUSSION

The major finding of our study indicate that RDW values are significantly correlated with CHA2DS2-VASc score among patients who have non- valvular atrial fibrillation , while also being independent predictor of high CHA2DS2-VASc score. . A RDW value of >13.4 was predictive of an augmented CHA2DS2-VASc score with 84% sensitivity and 90% specificity.

Several thromboembolic risk factors that are components of the CHA2DS2-VASc scores such as peripheral vascular disease, hypertension, Diabetes, stroke have been associated with increased RDW levels. Thus, patient with lone AF had less RDW value, hs-CRP serum , Creatinine serum , left atrial diameter ( LAD) and interventricular septum thickness (IVST) than non-lone AF patients.

In addition, patients with RDW > 13.4 had higher left atrium diameter (LAD), interventricular septum thickness (IVST), serum creatinine and hs-CRP serum than patients with RDW < 13.4

According to multivariate regression examination revealed that most significant independent predictors of thrmbo-embolic risk among non-valvular atrial fibrillation patients were Red cell distribution width (RDW) and high sensitive C- reactive protein serum level (hs-CRP).

The prevalence of AF is a common, which could be increment mortality and morbidity especially in old age. Ischemic cerebro-vascular stroke is the commonest serious form of thrombo-embolism that occurs on top of atrial fibrillation. [7]-[9] However, the occurrence of thrombo-embolism may depend on the coexisting clinical, echocardiographic, and laboratory parameters among patients have non-valvular AF. because that , multiple  risk scoring systems have been created  for the assessment  of thrombo-embolism risk by investigating coexisting factors among patients have non-valvular AF such as : clinical, echocardiographic and laboratory  factors. [10]-[13]. The CHA2DS2- VASc score is the most suggested risk scoring system for the evaluation of thrombo-embolism events. [5], [14].

The association between RDW value and CHA2DS2-VASc score can be explained by several mechanisms. Firstly, as in intermountain risk score research, the researchers consider RDW values (after conducting of long term follow-ups) as one of thromboembolic predictors among patients with non-valvular AF. (15), some previous studies confirm that relation like Kurt study and Tong study. Secondly, patients with AF have higher C- reactive protein and BNP (brain natriuretic peptide) serum levels comparably to controls. [16]-[19]., inflammation and oxidative stress that occur in top of some risk factors such as (diabetes mellitus, hypertension, aging and heart failure) may affect erythrocyte maturation. So, immature RBCs (red blood cells) go in the blood circulation incrementing their relative proportion to mature RBCs leading to the remarkable heterogeneity in their size [3].

In the end, the relation between included risk factors in CHA2DS2-VASc score and RDW has been revealed by prior studies [20]-[23]. RDW values are elevated among patients have heart failure comparably to control cases. While, the occurrence of decompensation events among patients who have heart failure are elevated in who had higher RDW values. [24], [25] In addition, RDW values are elevated among patients with history of cerebro-vascular ischemic stroke comparably to control cases. [20] Furthermore, elevated RDW is a significant predictor of cerebrovascular accidents in the general people and among patients who had cerebro-vascular ischemic stroke. [20]As well as, RDW has an association with diabetes and hypertension [22], [23] .So, Thrombo-embolism risk stratification is very important in terms of preventing adverse events in patients have non-valvular AF.

## CONCLUSION

We showed that RDW values were closely associated with thrombo-embolic risk assessed by CHA2DS2-VASc score among patients have atrial fibrillation. Consequently, it could be utilized with this score in thrombo-embolic risk stratification. In the end; we suggest more studies of multiple Centre study with larger number of patients needed in this setting.

**Limitations:**

Our study was a single-Centre study with small number of patients. In addition, chronic asymptomatic inflammatory or infectious diseases prevalent in developing Countries could not be excluded, which could be affect (RDW) values. Furthermore, Difference between RDW in both groups in our study could be simply reflection of significant age difference between both groups.so, further studies should be clarifying.

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