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CORRELATION BETWEEN RED BLOOD CELL DISTRIBUTION WIDTH AND B-TYPE NATRIURETIC PEPTIDE (BNP) IN PATIENTS WITH ACUTE CORONARY SYNDROME

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ABSTRACT

This study was undertaken to determine the correlation between brain natriuretic peptide (BNP) and red cell distribution width (RDW) in the acute coronary syndrome. It was done on hundred adult patients who were diagnosed with acute coronary syndrome and hospitalized in the Coronary care unit in Chettinad Hospital Research and Institute (CHRI), Kelambakkam. Patients were selected based on the inclusion criteria.

1) ST-segment elevation and ST-segment depression proven by electrocardiography.
2) Acute failure shows an ejection fraction less than 50% proven by echocardiography
3) Serum BNP levels > 400 pg/mL

Complete blood count and biochemical markers which include BNP, Troponin I, CPKMB were used for analyses within less than 24 hours of admission. The correlation between the three outcome variables and the explanatory variables was assessed by calculating correlation coefficients and its P-value and 95% CI. The study observations are as follows:

a) The mean age was older and there were more males in the ACS study group.
b) RDW showed statistically significant positive correlation with BNP levels (correlation coefficient 0.147, p value <0.001)
c) There was a weak positive correlation between Total leucocytes count and BNP levels (Correlation coefficient 0.013) and it was statistically not significant (P value 0.267).

To conclude, Elevated RDW levels is independently associated with a higher BNP level in patients with acute coronary syndrome. RDW has been proven to be as good as BNP.

KEY WORDS: **Brain Natriuretic peptide(BNP), red cell distribution width(RDW), Acute coronary syndrome**

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INTRODUCTION

Acute Coronary Syndrome

Acute coronary syndrome (ACS) is a conglomeration of clinical signs and symptoms due to myocardial ischemia. It encompasses some of the commonest life threatening conditions causing mortality in middle age and elderly population[1]. According to the 12 lead ECG at presentation

ACS can be categorized as

1. Acute ST-elevation myocardial infarction (STEMI)
2. Non–ST elevations ACS (NSTEACS) are patients who have ST-segment depression, T-wave changes, or no ECG abnormalities[1].
3. The term (NSTEACS) includes :
   a. Unstable angina
   b. Non–ST elevation myocardial infarction (NSTEMI) [1].

According to Global registry data, one month mortality rate ranges from "1.7% for patients with UA to 7.4% for patients with NSTEMI to 11.1% for those with STEMI" [2]. Therefore stratified early risk is critical for decision making for choosing the appropriate treatment, prompt invasive therapy and estimating the prognosis [3]. ECG helps in the clinical diagnosis of acute coronary syndrome and also aids in stratifying risk. However it has several disadvantages namely it fails to depict the posterior, lateral, and apical walls of the left ventricle and a normal ECG does not always completely rule out ACS[3]. Biochemical markers play a vital role in evaluating patients with chest pain and other symptoms suggestive of acute coronary syndrome. Cardiac-specific troponins T and I were used over CKMB which are highly accurate, sensitive, and specific indicators of myocardial ischemic injury [3].

However the impeding factors are that,

1. These levels rise after 6 hours after the onset of symptoms, therefore resulting in a false negative result for early myocardial ischemia.
2. Their usefulness in the detection of recurrent myocardial damage is restricted as the troponin levels remain elevated for an extended duration i.e. (up to 2 weeks) after myocardial necrosis

CK-MB has a shorter half-life and is more useful in the diagnosis of reinfarction and peri procedural MI [3]. Recently, studies have shown measurement of BNP to be a favourable predictor of prognosis and have been established to help in stratifying risks in patients with acute coronary syndromes [4-11].

Brain Natriuretic Peptide (BNP)

Natriuretic peptide hormones belong to a group of vasoactive peptides produced in the ventricular myocardium and responses to cardiac stretching and increased wall tension which leads to its release into the circulation [12]. This is directly correlated with both left ventricular filling[13] and pulmonary wedge pressure. B-type natriuretic peptide (BNP) is a cardiac marker for left ventricular dysfunction (cardiac failure) [14] has been proven as an important prognostic marker of acute coronary syndromes[11].

Red cell distribution width (RDW)

Red cell distribution width (RDW) is an estimation of variation in the size of circulating erythrocytes and the higher values indicates greater variation in cell sizes [16]. It is currently implicated as an important ancillary tool in the differential diagnosis of microcytic hypochromic anaemia. Recent studies have shown a strong association between higher RDW and increased risk of mortality due to cardiovascular events in both middle-aged and older adults. Higher RDW has been observed according to increase of age and rise in disease burden [17]. Therefore the objective of this study is to evaluate the correlation of B-type natriuretic peptide (BNP) and red cell distribution width in the acute coronary syndrome patients.

MATERIALS AND METHODS

The study was initiated after getting approval from Institutional Human Ethics Committee.

Type of Study

Prospective study

Number of Subjects

A single study group of 100 patients who are diagnosed with acute coronary syndrome. About 146 patients were selectively chosen from a total of 880 consecutive adult patients. The 46 patients were excluded for two main reasons:

- More than 24 hours between symptom onset and the time of blood sampling,
- Clotted blood sample or failure to request the laboratory study.

Place of study

Chettinad Hospital Research and Institute (CHRI), Kelambakkam.

The Duration of study

6 months from January 2014 to June 2014, The present study was possible with the collaboration with the Department of Cardiology at Chettinad Hospital Research and Institute (CHRI), Kelambakkam.

Patients were selected based on Inclusion Criteria

1) ST-segment elevation and ST-segment depression proven by electrocardiography.
2) Acute failure show ejection fraction less than 50% proven by echocardiography
3) Serum BNP levels > 400 pg /mL (BNP more than 400 pg /ml suggests diagnosis of heart failure)

Exclusion Criteria

1) Patients having Iron deficiency, B12 or Folate deficiency and Hemoglobinopathies
2) Patient who had recent episodes of haemolysis or haemorrhage
3) Patients who recently had blood transfusion
4) Patients who suffered from any inflammatory condition other than CVS
5) Pediatric patients aged 0-12 years.

6) Pregnant women

Sample collection

The period between the onset of ACS symptoms and the period of blood sampling should be less than 24 hours All the participants who participated in the study provided written informed consent. All the relevant clinical details including the age, sex, clinical presentation, RDW, BNP, Troponin I, CPKMB, complete blood count of the patients were noted. Venous blood samples were obtained from the participants for complete blood count and analysis of biochemical markers. The analyses were done within less than 24 hours of admission.

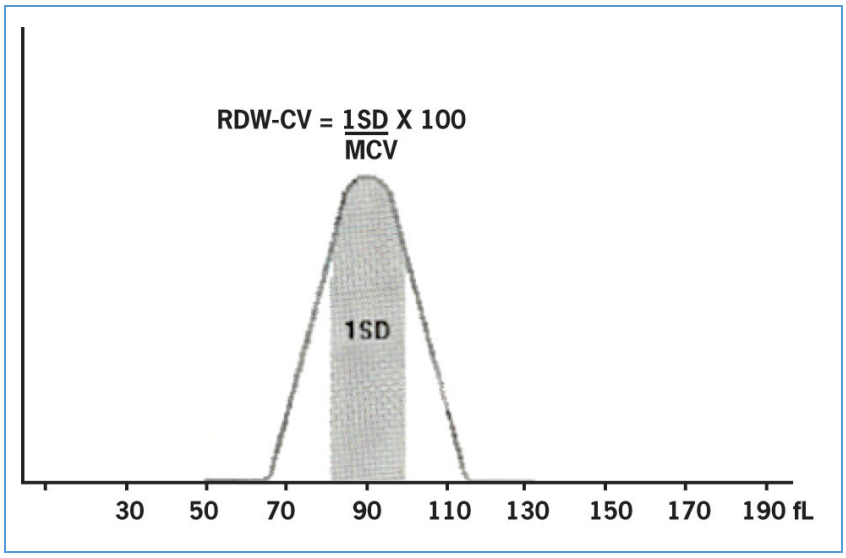
RDW

RDW and complete blood count are analysed according to Central Clinical laboratory, Department of Pathology, Chettinad Hospital Research and institute, Kelambakkam laboratory manual. RDW and complete blood count were analysed with the use of the Beckmann Coulter LH 780 Haematology Automated Analyser (Beckman Coulter, Inc . ,Miami, Florida).The Beckmann Coulter LH 780 Haematology Analyser is a fully automated haematology analyser system which is designed for in vitro diagnostic ,capable of analysing up to 110 samples per hour. About 100 µL venous blood sample is collected in vacutainer containing EDTA anticoagulant for the analysis of complete blood count, leukocyte, differential, nucleated red blood cell and reticulocyte count. The RDW is derived from pulse-height analysis and mathematically, it is the coefficient of variation (CV) in the percentage of the measurements of the red cell volume

RDW = (One Standard deviation of red cell volume ÷ mean cell volume) x 100 and is reported as a %.

The normal reference range for RDW in Pathology laboratory, Chettinad Hospital Research and institute, Kelambakkam is 11.5 to 13.5%.

Figure 1



BNP

BNP are analysed according to Central Clinical laboratory, department of Biochemistry, Chettinad Hospital Research and institute, Kelambakkam laboratory. Manual BNP was analysed with the use of Alere Triage which uses fluorescence immunoassay device to determine BNP in EDTA anticoagulant whole blood. The test procedure involves addition of several drops of EDTA anticoagulant - whole blood sample into the sample port on the test device. The sample of whole blood cells were separated from the plasma by using a filter and are then made to reacts with fluorescent antibody conjugates (Murine monoclonal and polyclonal antibodies) and allowed to flow into the test by capillary action. The complexes of each fluorescent antibody conjugates are caught by the discrete zones specific for each analyte. The meter (test device) is then entered into the Alere triage programmed to carry out the analysis after the specimen has reacted with the reagent. The analysis is established by the amount of fluorescence detected within 2 measurement zone. The concentration of the analytes in the specimen is directly proportional to the fluorescence detected. The normal reference range for BNP in this laboratory is <5pg/mL.[4]

Troponin I

Troponin I are analysed according to Central Clinical laboratory, department of Biochemistry, Chettinad Hospital Research and institute, Kelambakkam laboratory manual. Troponin I are analysed with Access Accu TnI assay which done in Beckmann Coulter Access Immunoassay system (2010 Beckman Coulter, Inc.). The Access Accu TnI assay is a both site immunoenzymatic ("sandwich") assay. The sample is added into the

reaction vessel along with monoclonal anti-cTnI antibody which will conjugated to alkaline phosphatase and paramagnetic particles coated with monoclonal anti-TnI antibody. The human cTnI combines to the anti-cTnI antibody on the solid phase, while the anti-cTnI antibody alkaline phosphatase conjugates and reacts with different antigenic sites on the cTnI molecules. After incubation in the reaction vessel, materials bound to the solid phase are placed in a magnetic field while unbound materials are washed away. Then, the chemiluminescent substrate Lumi-Phos 530 is added to the vessel and light generated by the reaction is measured with a illuminometer. The light production is directly proportional to the concentration of cTnI in the analysed sample. The amount of analyte in the sample determined from a stored, multi-point calibration curve. The normal reference range for Troponin I in this laboratory is 0.0ng/mL.[6]

CPK-MB

CPK-MB are analysed according to Central Clinical laboratory, department of Biochemistry, Chettinad Hospital Research and institute, Kelambakkam laboratory manual. CPK-MB are analysed with Dimension MBI method which is a modification of the international federation of clinical chemistry(IFCC) creatine kinase (CK) primary reference 37^0C procedure, adapted for use on Dimension clinical chemistry system (Siemens Healthcare Diagnostic Inc., Frimley, Camberley, United Kingdom). The activity of the B subunit of creatine kinase MB isoenzyme is not inhibited and it is on this basis that CPK-MB can be measured. In an enzyme coupled reaction, creatine kinase in patient's samples catalyzes the transphosphorylation of creatine phosphate to adenosine-diphosphate (ADP), Hexokinase (HK) uses the ATP to phosphorylate glucose. The resulting glucose-6-phosphate is oxidized by glucose-6-phosphate dehydrogenase (G-6-PDH) with the simultaneous reduction of nicotinamide adenine dinucleotide phosphate (NADP) to NADPH. The rate of formation of NADPH is measured bichromatically at 340, 540nm and is directly proportional to CK-B activity in the sample. The calculation of the relative percentage of CK-MB isoenzyme activity in the total CK activity. The normal reference range for CPK-MB in this laboratory is 7-25 U/L.[1]

RESULTS

STATISTICAL ANALYSIS

Statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA) software. BNP, CPKD and TROP levels were considered as primary outcome variables. RDW, WBC parameters and sociodemographic variables were taken as explanatory variables. Descriptive analysis of all the explanatory and outcome parameters was done. Categorical variables were presented in frequencies and also in percentages. The numerical variables presented in Means and Standard deviations. The correlation between the three outcome variables and the explanatory variables was assessed by calculating correlation coefficients and its p-value and 95% CI. Graphical representation the data also presented in an appropriate way.

RESULTS

Between January 2014 to June 2014, 880 patients were admitted in Coronary care unit (CCU), 146 acute coronary syndrome patients were included in the study based on the inclusion criteria and among them 46 patients were excluded due to delay blood sampling and clotted blood samples. Therefore a total of 100 participants participated in the study. The age of the participants ranged from 32 to 86 years, with a mean age of (56.53±11.166) years (Table 1). Males constituted, 67(67%) of the study subjects and females constituted the remaining 43(43%) of study subjects. (Table 2) However, the mean age was older and there were more males in the ACS study group. Descriptive analysis of all the red blood cell related parameters of the study population are presented in table 3. The mean haemoglobin level was 12.53 gm/dl with a standard deviation of 2.4 gm/dl and the mean values of all the other blood parameters were within the normal biological range. RDW showed statistically significant positive correlation with BNP levels (correlation coefficient 0.147, p value <0.001). This was further highlighted in the scatter gram [Fig-1] which shows increasing RDW values with increasing BNP values.

Descriptive analysis

1) Total of 100 participants were participated in the study. The age of the participants was ranging from 32 to 86 years and the mean age was 56.5 years.

Table 1
Descriptive analysis of Age (N=100)

Parameter	Mean±STD	Median	Max	Min	95% C.I.for EXP(B)	
					Lower	Upper
Age	56.53±11.2	56.00	86.0	32.0	54.31	58.75

2) Males constituted, 67(67%) of the study subjects and females constituted the remaining 33(33%) of study subjects.

Table 2
Descriptive analysis of gender (N=100)

Sex	Frequency	Percent
Male	67	67%
Female	33	33%
Total	100	100%

3) Descriptive analysis of the red blood cell related parameters of the study group are presented in table 3. The mean haemoglobin level was 12.53 gm/dl with a standard deviation of 2.4 gm/dl and mean red cell distribution width was 15.02% with a standard deviation of 1.41%. The mean values of all the other RBC parameters were within the normal biological range.

Table 3
Descriptive analysis of RBC Parameters (N=100)

Parameter	Mean±STD	Median	Max	Min	95% C.I.for EXP(B)	
					Lower	Upper
Red Blood cell count (million/cmm)	4.371±0.67	4.44	6.37	2.41	4.24	4.5032
Haemoglobin (g/dl)	12.530±2.4	12.60	17.50	15.15	12.05	13.01
MCV (FL)	86.954±7.3	86.60	106.9	69.0	85.50	88.78
MCH (pg)	28.726±7.1	28.73	34.8	21.4	28.20	29.25
MCHC (g/dl)	33.084±0.9	33.10	36.3	31.0	33.91	33.26
PCV (%)	38.219±6.4	38.25	53.4	21.8	36.95	39.49
Red cell distribution width (%)	15.020±1.4	14.80	21.3	12.4	14.74	15.30

4) The mean Total leucocyte count was 11,711 cells/cmm with a standard deviation of 4945 cells/cmm and the mean platelet count was 2.72 lakhs/dl with a standard deviation of 1.43lakhs/dl.

Table 4
Descriptive analysis of WBC & platelet Parameters (N=100)

Parameter	Mean±STD	Median	Max	Min	95% C.I.for EXP(B)	
					Lower	Upper
Total count (cells/cmm)	11711±4945.5	10550	35500	5300	10729.70	12692.30
Platelet count (lakhs/dl)	2.7227±1.44	2.6050	14.80	0.11	2.437	3.008

5) The descriptive analysis of all the outcome parameters

The mean BNP level was 866.71(pg/mL) with a standard deviation of 564.8. The mean TROP and CPKMB levels were 1.84 and 46.44 respectively.

Table 5
Descriptive analysis of Other Parameters (N=100)

Parameter	Mean±STD	Median	Max	Min	95% C.I.for EXP(B)	
					Lower	Upper
B-type Natriuretic Peptide (pg/mL)	866.71±564.87	759.0	4600	401	754.63	978.79
TROP (ng/mL)	1.84±5.68	0.055	31.66	31.65	0.7132	2.97
CPKMB (U/L)	46.45±25.62	43.00	198.0	2.6	41.362	51.53

6) Association of RDW and BNP in study population (n=100)

There was a statistically significant positive correlation between Red cell distribution width and BNP levels (correlation coefficient 0.147, p value <0.001)

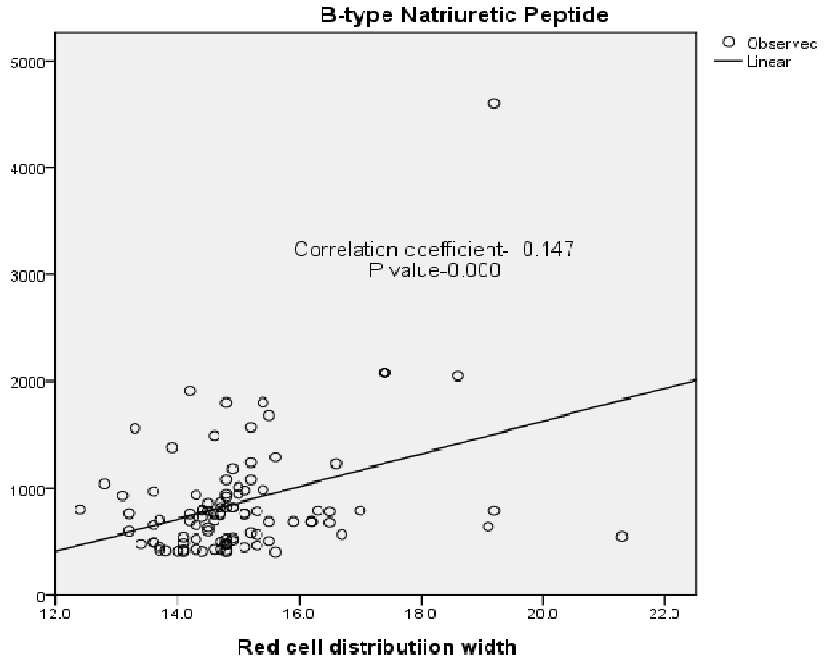


Figure 2
Red cell distribution width and BNP levels

7) Association of RDW and TROP

There was slight negative correlation between Red cell distribution width and TROP levels (correlation coefficient 0.147, p value 0.05) and this negative correlation was statistically significant.

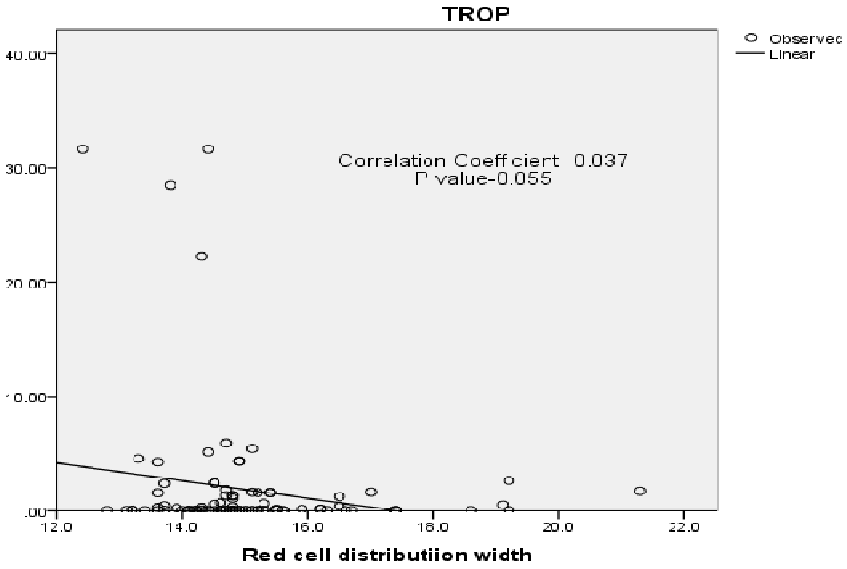


Figure 3
Red cell distribution width and TROP levels

DISCUSSION

The present study was to observe a correlation between B-type Natriuretic peptide and red cell distribution width in acute coronary syndrome. The study was done on 100 adult patients who were diagnosed with acute coronary syndrome, selectively chosen from a total of 880 patients who were hospitalized in the Coronary care unit in Chettinad Hospital Research and Institute (CHRI), Kelambakkam. The study result suggests the measuring of RDW level may provide valuable prognostic information for acute coronary syndrome patients who come to the Emergency department with chest discomfort. The study found an independent correlation between the RDW levels and adverse outcome in acute coronary syndrome patients. Red cell distribution width (RDW) is a quantifiable measure of variability in the size of circulating erythrocytes with higher values demonstrating the greater heterogeneity in the red blood cell sizes [22] RDW first gain important by Price jones in 1910 who found correlation between red cell anisocytosis and diseases [23]. Bessman et al studied RDW along with mean corpuscle volume used in classification of red cell disorders [22]. Zalawadiya, et al stated "Red blood cells may represent as a 'real-time' biomarker of an underlying abnormal pathophysiologic state"[24]. The age of the participants in the present study population was ranging from 32 to 86 years, with a mean age of 56.5 years. Patel et al studied the relationship between RDW and mortality in adults age 45yrs and older the study observed RDW increases with age which may be attributed to oxidative stress and inflammation and concluded RDW as an "strong predictor of mortality in the general population of adults aged 45 and older"[25]. This study has excluded pediatric age groups. According to Vural Polat et al and Jianping Chen et al who did similar studies in pediatric age groups and concluded that RDW could be used as an important prediction of morbidity and mortality [26,27]. There were more males than women in the present study group. Zalawadiya et al studied "Gender and ethnic differences in RDW and its association with mortality among low risk healthy United states adults" and concluded that men have a greater risk of mortality than women and no modification effect was observed by ethnicity [24]. In present study group, patients who having Iron deficiency, B12 or Folate deficiency, Hemoglobinopathies, recent episodes of haemolysis or haemorrhage, recent blood transfusion and any inflammatory condition were excluded.. The scope of RDW implication widened and it was found to be useful as a prognostic tool in MI, PHT, Stroke, Heart failure and acute coronary syndrome[28-31]. Felker et al analysis 2 large groups of patients with Heart failure and reported high RDW levels had a strong independent association with adverse outcome[32]. Uyarel et al studied 2506 patients having ST-segment elevation myocardial infarction (STEMI) and found elevated RDW at the earlier stage of myocardial infraction were associated with adverse outcomes [33]. Karabulut et al and Tanboga et al studies reported elevated RDW level showed a related association with thrombus burden, poor reperfusion, in-hospital mortality, and long-term mortality in patients having ST-segment elevation myocardial infarction (STEMI) and treated with PCI [34-35]. Tanboga et al in another study reported that higher level of RDW was an independent prognosticator of impaired coronary collateral circulation in non ST-segment elevation myocardial infarction patients [36]. Another study has reported higher RDW levels were prognosticator of any mortality in a 2-year follow-up in patients with angiographically detected CAD, including acute coronary syndrome[13]. The present study observed elevated BNP values were associated with higher RDW level and also shown a significant positive correlation (correlation coefficient value = 0.147 and P value = 0.000) between red cell distribution width and B-type Natriuretic peptide. Felker et al and Van Kimmenade et al have reported in their studies in patients with heart failure that RDW was as good as NT-pro-BNP and superior to New York Heart Association class, renal function and even ejection fraction in predicting outcomes[37-38]. According to these aspect, may explain the significant positive correlation between RDW and BNP in ACS patients

CONCLUSION

From the present study it has been concluded that elevated RDW levels is independently associated with a higher BNP level in patients with acute coronary syndrome. RDW has been proven to be as good as BNP. Red Blood Cell Distribution Width is a simple freely available test and comes as a part of complete blood count which is affordable to all socioeconomic groups. RDW can be also used as one of the prognostic cardiac marker in patients with Acute Coronary Syndrome.

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