

Red Cell Distribution Width as a Marker of Disease Severity and In-hospital Mortality in Patients with ST-segment Elevation Myocardial Infarction

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ABSTRACT

Background: The red cell distribution width (RDW) has been investigated as a predictive factor for complications and mortality in several critical illnesses, including cardiovascular diseases.

Objective: The current study aimed to assess the relationship of RDW with severity and in-hospital mortality in patients with ST-elevation myocardial infarction (STEMI).

Materials and methods: A prospective hospital-based observational study was conducted at a tertiary care institute of Northern India. Fifty patients of STEMI who underwent coronary angiography/primary coronary intervention were enrolled as cases and equal number of age- and sex-matched individuals not suffering from any cardiac disease were taken as controls. The RDW admission values of the cases were compared with that of controls. Red cell distribution width values were also compared across the outcome groups among cases.

Results: The mean RDW-SD of the cases was 49.0 ± 4.6 fL whereas it was 44.7 ± 3.5 fL for controls, the difference being statistically significant ($p < 0.001$). Among the total patients, 4 (8.0%) expired during hospital stay and the rest 46 (92.0%) were discharged alive. The mean RDW-SD of expired patients was significantly higher than that of patients who remained alive ($p = 0.002$). There was a significant positive correlation between RDW and global registry of acute coronary events (GRACE) score ($p = 0.02$) and a significant negative correlation between RDW and left ventricular ejection fraction (LVEF) ($p = 0.04$). Area under the receiver operating characteristics (ROC) curve for RDW was higher than that of LVEF, showing superiority of RDW to LVEF in predicting mortality among the STEMI patients.

Conclusion: Red cell distribution width may serve as a promising prognostic biomarker and tool for risk stratification in patients with STEMI.

Keywords: Disease severity, In-hospital mortality, GRACE score, Predictor, Red blood cell distribution width, ST-elevation myocardial infarction.

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HIGHLIGHTS

The red cell distribution (RDW) admission values of patients with acute ST-elevation myocardial infarction (STEMI) was significantly higher than that of healthy controls, implying significantly elevated level of RDW in STEMI. Further, RDW values increased as the disease severity increased among the cases. The RDW admission values of patients who later expired were found to significantly higher than the RDW values of patients who were discharged alive. Significant positive correlation was found between the RDW admission values and the global registry of acute coronary events (GRACE) score ($r = 0.443$, $p = 0.02$) and a significant negative correlation between RDW admission value and left ventricular ejection fraction (LVEF) ($r = -0.15$, $p = 0.04$).

INTRODUCTION

Despite tremendous progress in their diagnosis and management over the past 40 years, cardiovascular diseases (CVDs), which includes myocardial infarction (MI), remains the top most cause of mortality and disability globally.¹ Despite the value of the conventional risk factors, identification of possible new risk factors may aid in risk stratification and targeted MI prevention.² Red blood cells (RBCs), also known as erythrocytes, are part of thrombi and blood clots that naturally form in the body. However, little is known about how red blood cells' intrinsic characteristics may affect the chance of developing CVDs.³

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Red cell distribution width a unit to assess the variation in the size of circulating RBCs, is routinely mentioned as a component of the standard blood cell count examination.⁴ Classically, RDW and mean corpuscular volume (MCV) are employed in the differential diagnosis of anemia, especially when the anemia is characterized by either small or large RBCs. An elevated RDW can also occur due

to factors that alter the shape and size of RBCs, caused by the early release of the immature RBCs, known as reticulocytes, into the bloodstream.⁵ Red cell distribution width has been found to be an invaluable indirect biomarker of inflammation along with oxidative stress.^{6,7} Both Inflammation and oxidative stress have a major role in the growth and development of unstable plaques, causing their rupture and subsequent thrombosis.^{8,9} As per the National Health and Nutrition Examination Survey (NHANES), a representative survey of the US population, individuals with RDW values exceeding the 75th percentile were grouped in the highest 10-year Framingham risk group for coronary artery disease (CAD).¹⁰ Studies conducted on patients with cardiac diseases have indicated that RDW can predict all-cause mortality, cardiovascular morbidity as well as mortality, and negative outcomes in those suffering from heart failure.^{11–18} Beyond heart disease, it has been found to forecast mortality in adult acute kidney injury (AKI) patients with the need for renal replacement therapy (RRT) and also act as a predictor of outcome in severe sepsis.^{19,20}

A comprehensive review of literature shows that a raised RDW is a robust and independent predictor of incident MI, and prognosticator in coronary heart diseases.^{2,13,14,21} But till date, only a limited number of studies have evaluated the relationship of RDW with in-hospital outcomes including mortality among patients suffering from STEMI.^{22,23} The current study aimed to find the association of RDW admission value with disease severity and in-hospital outcomes including mortality in patients diagnosed with STEMI. Red cell distribution width admission value could serve as an early, cost-effective, and easily accessible biomarker to identify high-risk patients, potentially guiding therapeutic decisions and resource allocation in critical care settings. If an association is established, RDW could become a practical tool to complement traditional risk stratification methods, facilitating the early identification of individuals at greater risk for severe complications and mortality. This study's findings will impart important understandings into the utility of RDW in acute management of STEMI and could potentially usher in improvements in clinical decision-making, patient monitoring, and outcomes.

MATERIALS AND METHODS

Study Population, Design, and Settings

A longitudinal observational study was performed among patients diagnosed with STEMI and admitted to the Department of Cardiology of a tertiary care institution in North India, between April 2021 and September 2022. The strengthening the reporting of observational studies in epidemiology (STROBE) guidelines were followed to ensure the reporting of this observational study.

Inclusion Criteria

- Patients with ST elevation changes on electrocardiography (new ST segment elevation at the J point in at least two contiguous leads of ≥ 2 mm (0.2 mV) in men or 1.5 mm (0.15 mV) in women in leads V2-V3 and/or of ≥ 1 mm (0.1 mV) in other contiguous chest leads or the limb leads) or left bundle branch block (LBBB) of recent onset.
- Cardiac enzyme positive (TROP-T/CPK-MB).
- Undergoing coronary angiography/primary coronary intervention (PCI).

Exclusion Criteria

- Patients with anemia (Hb <13 gm in males, Hb <12 gm in females).

- Patients <18 years and ≥ 80 years of age.
- Presence of chronic diseases such as chronic kidney disease, chronic liver disease, diabetes, and malignancy.

Study Procedure

Patients with STEMI fulfilling the inclusion and exclusion criteria were recruited in the study. The hospital has around 100–150 cases of acute MI admitted in a year and half of them are STEMI. Therefore, based on feasibility a sample size of 50 cases of STEMI was taken.

Selected patients underwent detailed clinical history and examination. Following investigations were conducted on all the recruited patients on admission: Electrocardiography, complete blood counts, liver function test, kidney function test, TROP-T or CPK-MB.

The blood samples were collected immediately (after hospital admission) in tri-potassium ethylenediaminetetraacetate (K3 EDTA) vials for RDW measurement. Samples for RDW measurements were immediately sent to the laboratory and analyzed within 4 hours by Sysmex Transasia hematological analyzer using fully automated fluorescence microscopy. Subsequently, coronary angiography was done. According to the angiography findings, patients were categorized into single vessel disease (SVD), double vessel disease (DVD), and triple vessel disease (TVD). All the patients were to follow the routine protocol and standard guidelines for managing acute MI. Global registry of acute coronary events risk scoring was performed for all the patients within 24 hours of admission. It is one of the most widely used risk-stratification tools for predicting in-hospital mortality in acute coronary syndrome (ACS) patients that gives an aggregated scoring scheme for STEMI as well as non-STEMI and includes eight parameters of the patient: – age, sex, systolic blood pressure, heart rate, ST – segment changes, presence of cardiac arrest at presentation, raised cardiac biomarkers and serum creatinine level.²⁴ As per the aggregated scores, patients are categorized as low risk (GRS ≤ 108), Intermediate risk (GRS 108–140), and high risk (GRS ≥ 141).²⁴

In all the patients, 2D Echocardiography was also performed at admission. Patients were then followed during the hospitalization for major adverse cardiovascular events (MACE) like reinfarction, repeat percutaneous transluminal coronary angiography (PTCA) arrhythmias, and cardiac arrest. The end point of the follow-up was either patient's mortality or discharge from hospital.

For comparison of RDW admission values of the STEMI patients with healthy individuals, 50 age (± 3 years) and sex-matched controls were taken out of the general medicine OPD having no history of coronary heart disease and having normal ECG findings.

Statistical Analysis

Statistical analysis was performed out using Statistical Package for Social Sciences software, version 24.0 of IBM. Continuous variables were summarized as means with standard deviations (SD) whereas categorical variables were exhibited as frequencies with percentages. Unpaired/student *t*-test or analysis of variance (ANOVA) were used to compare continuous variables, whereas Chi-square/Fischer exact tests was used to compare categorical variables. Correlation of two continuous variables were examined through Pearson (*r*) correlation coefficient. Receiver operating characteristics (ROC) curve analysis and calculations of the area under the curve (AUC) for LVEF and RDW were performed to compare their predictability for in-hospital mortality.

RESULTS

A total of fifty patients of STEMI who have undergone coronary angiography/PCI were enrolled and their RDW values were compared against 50 age- and sex-matched healthy controls. No significant differences were observed in the mean age or gender distribution of the two groups and their hemoglobin levels were found to be similar. However, the mean RDW-SD of the cases were significantly higher than that of controls ($p < 0.0001$) (Table 1).

On electrocardiography, majority (70%) of the cases had anterior wall- followed by inferior wall-MI (24.0%) with one (2.0%) each having anterolateral wall, inferolateral, and lateral wall-MI (Fig. 1).

On coronary angiography of the cases, 21 (42%) had SVD, 18 (36%) had DVD and rest 11 (22.0%) had TVD.

Mean GRACE risk score of the cases was 130.1 ± 40.3 , with 18 (36.06%) patients coming in the high-risk, 24 (48.0%) in the intermediate risk, and 8 (16.0%) in the low-risk group.

Among the parameters assessed for their relationship with severity of the disease as per the angiography findings, significant

Table 1: Baseline characteristics of the patients with STEMI, the cases and healthy controls ($n = 100$)

| Variables | Cases ($n = 50$) | Controls ($n = 50$) | p -value |
|---------------------|--------------------|-----------------------|------------|
| Mean age (in years) | 54.8 ± 10.6 | 53.2 ± 8.5 | 0.84 |
| Gender | No. (%) | No. (%) | |
| Male | 10 (20.0) | 10 (20.0) | 1.0 |
| Female | 40 (80.0) | 40 (80.0) | |
| Mean Hb (in gm/dL) | 14.1 ± 4.6 | 14.2 ± 4.7 | 0.93 |
| Mean RDW SD (in fL) | 49.0 ± 4.6 | 44.7 ± 3.5 | <0.0001 |

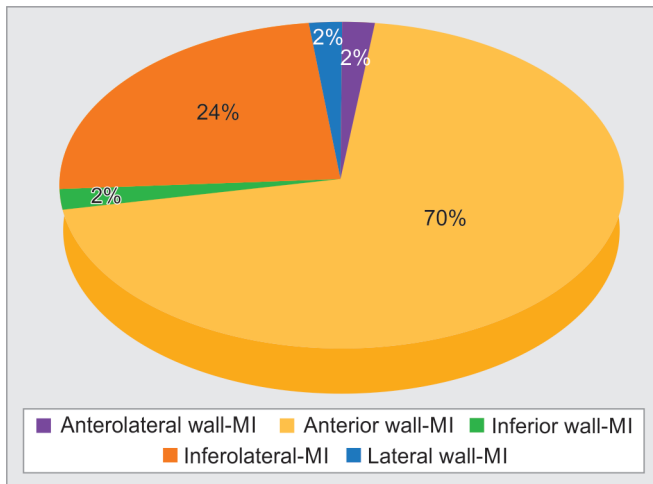


Fig. 1: Distribution of the cases as per the echocardiography findings

Table 2: Association of various parameters with disease severity among patients with STEMI ($n = 50$)

| Parameter | SVD [#] | DVD [#] | TVD [#] | p -value | Post-hoc Bonferroni |
|-----------------------|------------------|------------------|------------------|------------|---------------------|
| | Mean \pm SD | Mean \pm SD | Mean \pm SD | | |
| Age (in years) | 52.5 ± 10.9 | 56.9 ± 11.2 | 56.5 ± 8.5 | 0.367 | NS |
| RDW-SD (in fL) | 44.8 ± 3.9 | 48.0 ± 5.5 | 52.8 ± 4.4 | 0.013* | a*b; b*c; a*c |
| Hemoglobin (in gm/dL) | 14.6 ± 1.7 | 13.7 ± 1.3 | 13.8 ± 1.0 | 0.110 | NS |
| GRACE score | 125.0 ± 29.8 | 139.5 ± 32.5 | 125.0 ± 16.4 | 0.256 | NS |
| LVEF (%) | 48.6 ± 11.2 | 45.1 ± 13.4 | 44.7 ± 13.4 | 0.588 | NS |

[#]SVD, single vessel disease; DVD, double vessel disease; TVD, triple vessel disease. *Statistically significant

increase in mean RDW-SD value ($p = 0.013$) from SVD to TVD was found, implying higher RDW-SD is associated with increased severity of the disease. Rest all parameters like age, Hemoglobin level, GRACE score and LVEF were not found to be associated with the severity (Table 2).

A total of 4 (8.0%) patients died during the in-hospital stay, and the rest 46 (92.0%) were discharged alive (Table 3). Among the various parameters assessed for association with the outcome (alive/died), mean RDW-SD and GRACE score were significantly higher and mean LVEF was significantly lower in patients who expired compared to patients remaining alive, implying RDW-SD, GRACE score and LVEF are associated with the outcome. The rest other parameters were found to be non-significant (Table 3).

Pearson's correlation coefficient (r) used to find correlation of RDW SD between GRACE score gave a value of 0.443 ($p = 0.02$) implying a moderate positive correlation between the two variables (Fig. 2A). Similarly, the value of r for correlation between RDW SD and LVEF was -0.15 ($p = 0.04$) implying a weak negative correlation between RDW SD and LVEF (Fig. 2B).

Comparison of ROC Curves showed that AUC of RDW SD was 0.514 (95% CI: 0.197–0.832, $p = 0.026$) whereas AUC of LVEF was 0.185 (95% CI: 0.040–0.329, $p = 0.038$) implying RDW-SD is superior to LVEF in predicting the in-hospital mortality (Fig. 3).

DISCUSSION

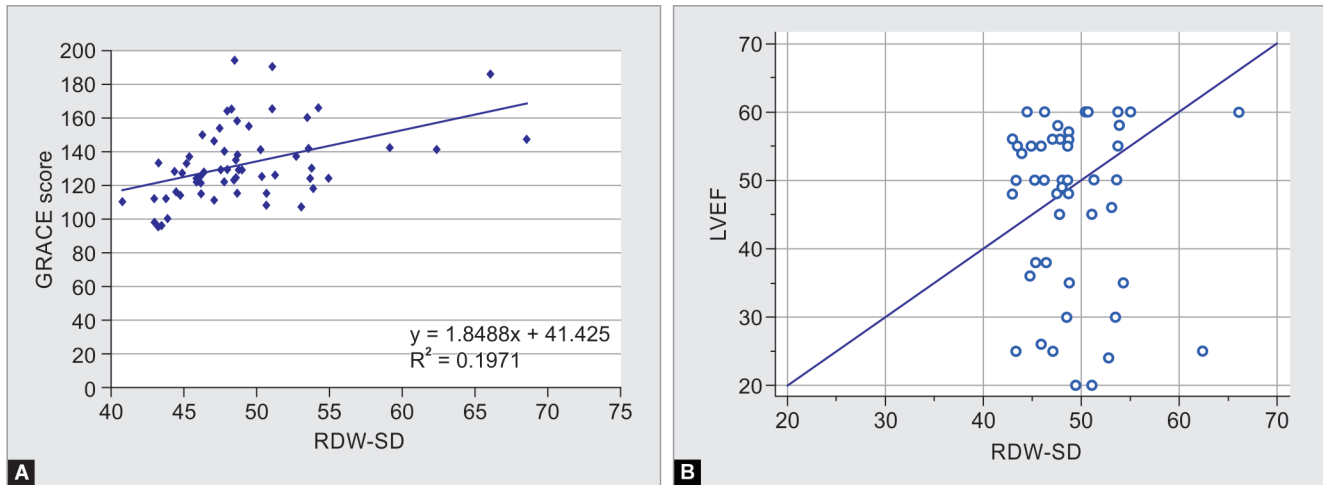
Due to speedy economic development and subsequent lifestyle changes, acute STEMI has now a substantial mortality and morbidity rate in developing countries like India. Even after significant advancements in diagnostic medicine, there is a lack of readily available biomarkers to rapidly detect the high-risk populations for death due to acute MI. In this current study, we aimed to assess the relationship between RDW admission value and disease severity and outcome among patients with STEMI who presented at a large tertiary care institute in Northern India.

In our study, fifty patients of acute STEMI undergoing angiography/PCI admitted at our institution were included.

Table 3: Association of various parameters with in-hospital mortality in patients with STEMI ($n = 50$)

| Parameter | Alive ($n = 46$) | Expired ($n = 4$) | p -value | t -test |
|-----------------------|--------------------|---------------------|------------|-----------|
| | Mean \pm SD | Mean \pm SD | | |
| Age (in years) | 55.4 ± 10.6 | 48.0 ± 8.7 | 0.184 | 1.34 |
| RDW-SD (in fL) | 48.8 ± 4.3 | 56.6 ± 8.0 | 0.002* | 3.231 |
| Hemoglobin (in gm/dL) | 14.1 ± 1.4 | 14.9 ± 1.9 | 0.327 | -0.989 |
| LVEF (%) | 47.8 ± 11.9 | 34.3 ± 10.9 | 0.03* | 2.190 |
| GRACE score | 128.7 ± 29.6 | 165.5 ± 15.2 | 0.01* | 2.418 |

*Statistically significant



Figs 2A and B: (A) Pearson's correlation of RDW-SD with GRACE score among STEMI patients; (B) Pearson's correlation of RDW-SD with LVEF among STEMI patients

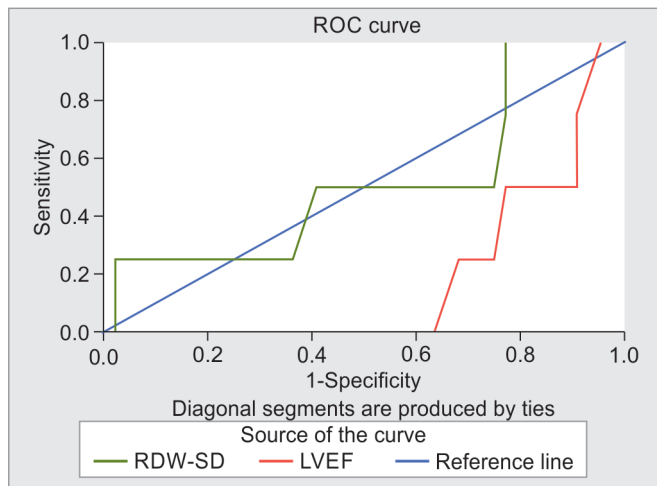


Fig. 3: Receiver operating characteristics curve comparing the area under the curve (AUC) for RDW-SD and LVEF for predicting in-hospital mortality among STEMI patients

The majority of the patients had anterior wall MI (70.0%) and had SVD (42.0%). The mean RDW-SD value of patients with STEMI was found to be significantly higher compared to that of healthy controls ($p < 0.001$). Higher RDW-SD values were found to be associated with the more severe disease/increased degree of coronary stenosis. A study conducted by Nagula et al.²⁵ assessing the correlation between RDW levels and the degree of CAD, found that RDW SD and RDW CV levels of patients with CAD were significantly elevated compared with those of patients without CAD. The RDW SD and RDW CV values showed significant positive correlation with modified Gensini score, a marker of severity of coronary stenosis on angiography and RDW was proved to be an independent forecaster for the severity of CAD, similar to our finding. A study by Feng-Lian et al.²⁶ came up with similar findings and found that RDW is associated with presence and the severity of coronary stenosis both, signifying that it might prove to be an easily available marker for the prediction of CAD and its severity.

In our study, RDW SD values at admission were found to be significantly higher in patient having mortality during the hospital

stay compared to that of patients who remained alive and were discharged, implying elevated RDW value is associated with higher in-hospital mortality in patients with STEMI. Further, RDW SD values had a moderate positive correlation with the GRACE score ($r = 0.443$, $p = 0.02$). A study by Shivalinga et al.²⁷ assessing the relationship of RDW values with the clinical outcome of 100 Patients having ACS found that 32 out of the 36 patients having arrhythmia had high RDW, and all 36 study subjects having repeat angina had high RDW.

A study by Fu et al.²⁸ to evaluate the value of RDW for predicting in-hospital mortality among patients having ACS found that RDW of patients having in-hospital death was significantly greater than that of in-hospital survivors [14.3 (13.7, 14.8) vs 13.4 (12.8, 13.9), $p < 0.001$] similar to our finding and RDW was an independent predictor of in-hospital mortality (OR 1.357, 95% CI: 1.067–1.724, $p = 0.013$). Compared with the GRACE risk score, inclusion of RDW improved the AUC from 0.866 (95% CI: 0.821–0.911) to 0.882 (95% CI: 0.838–0.926) ($p = 0.035$) implying RDW added to the predictive value of GRACE risk score for in-hospital mortality. Similarly, a study by Polat et al.²⁹ evaluating the relationship between RDW and GRACE score among patients having unstable angina and non-STEMI found that elevated RDW values were associated with higher in-hospital death ($p = 0.001$) and a significant positive correlation was found between RDW values and GRACE scores ($p < 0.001$), also observed in our study. In another study by Sangoi et al.³⁰ assessing the prognostic value of RDW among patients with acute MI, RDW was found to be an independent predictor for in-hospital death (HR–1.358, 95% CI: 1.04–1.77; $p = 0.023$).

Apart from the predictability of RDW for short-term or in-hospital mortality, studies have shown that RDW could also predict long-term mortality among STEMI patients.^{28,29} A research study by Arbel et al.³¹ revealed that a RDW value exceeding 14% is independently linked to a heightened risk of long-term all-cause mortality in patients with STEMI who underwent primary coronary intervention (PCI), whereas Lin et al.³² showed that RDW along with neutrophil to lymphocyte ratio (NLR) are independent predictors of long-term cardiovascular death among the STEMI patients.

The factors possibly contributing to the elevated RDW among STEMI patients are linked with the pathophysiology of endothelial injury and atherosclerosis. These leads to a reduced half-life of

the RBCs, which generates an increase in the peripheral movement of reticulocytes with the effect of an increased RDW.^{3,4,33–36}

Oxidative stress, along with inflammation and the cytokines released as a result of inflammation, inhibits iron metabolism. This disruption shortens the lifespan of RBCs and impedes their maturation. Additionally, it accelerates the release of reticulocytes i.e. immature RBCs, into the circulation while diminishing the bone marrow's response to erythropoietin. Consequently, this chain of events results in an elevated RDW.^{3,4,33,34,36}

Limitations

This study has some limitations. Firstly, the sample size was small, limiting the generalizability of the findings. The fluctuations in the RDW values, when doing serial RDW measurements, were seen. Furthermore, we did not take into account other inflammatory biomarkers that could play a role in anisocytosis. The research was conducted on a high-risk population, limiting its generalizability, and as with all observational studies, causal inferences can't be made. It is also unknown from the study whether RDW values would be able to predict the outcome in STEMI patients who are low-risk or have anemia. Further, RDW values are not specific to STEMI and is having been found to be increased in a number of conditions, including hypertension, ischemic cerebrovascular diseases, atrial fibrillation (AF), heart failure (HF) and peripheral artery disease (PAD).³⁷ Apart from cardiovascular diseases, chronic diseases such as diabetes, chronic kidney diseases, chronic liver disease, and cancer can also lead to increased RDW. However, such patients fell under the exclusion criteria of the study.

CONCLUSION

In conclusion, our study shows that the RDW admission value can predict the severity and in-hospital mortality in STEMI patients undergoing coronary angiography. The RDW provides us a convenient and inexpensive risk stratification tool at the time of admission in acute coronary artery disease patients and decision-making tool for their management. Further, well-designed prospective large scale multicentric studies are required to be conducted in order to establish the predictive ability of RDW admission value for in-hospital mortality in patients with STEMI.

We recommend that clinicians and intensivists should be mindful of the prognostic value of RDW for the mortality risk in STEMI patients and the RDW admission value should become a biochemical marker of the standard assessment for STEMI. Serial monitoring of RDW levels and RDW-related comorbidities may need to be studied further.

DECLARATIONS

Ethics Approval

The study was approved by Institute Ethics Committee (IEC), MM Institute of Medical sciences & research, Mullana, Ambala, India (Protocol no. 1985/2021 dated 21-02-2021).

Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

RR and SG: Experiments concept and design; RR: Experiments performing; RR, NG and SS: Analysis and interpretation of

experiments results. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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