

# Red Cell Distribution Width and Elongation Index in a Cohort of Patients With Juvenile Acute Myocardial Infarction

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## Abstract

In a cohort of patients with juvenile myocardial infarction, we considered the red cell distribution width (RDW), hematocrit, hemoglobin, and elongation index values at the initial phase and at 3 and 12 months from the acute event. In the initial phase, only the elongation index values turn out reduced if compared with those of the control group, and that only turn out to discriminate the infarcted ST-segment elevation myocardial infarction (STEMI) from non-STEMI. Dividing the patients according to the traditional risk factors and the extent of coronary heart disease, there are no significant variations in the analyzed parameters. No major changes are observed after 12 months from the acute event. Both to 3 and to 12 months from the infarct episode, the negative statistical correlation between RDW and the value of elongation index remains. These data make us reflect on the role of the degree of anisocytosis of red blood cell expressed by the RDW on the determinism of erythrocyte deformability, which plays its role in the microcirculation district and that is essential in the transfer of tissue oxygen.

## Keywords

red blood cell distribution width, elongation index, erythrocyte deformability, juvenile acute myocardial infarction

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## Introduction

As part of the “Sicilian study on juvenile myocardial infarction,” we have reported in recent years about the aspects regarding the hemorheological profile,<sup>1</sup> the metabolic and functional activity of polymorphonuclear leukocytes<sup>2,3</sup> and platelets,<sup>4,5</sup> the role of genetic polymorphisms,<sup>6</sup> oxidative stress,<sup>7</sup> protein oxidation,<sup>8</sup> the neutrophil/lymphocyte ratio,<sup>9</sup> and plasma viscosity<sup>10</sup> at the initial phase and in the months following the infarct event. However, we have not disregarded neither the behavior of erythrocyte deformability nor the red cell distribution width (RDW), although in part of the entire cohort of these patients, we have previously observed a reduction in erythrocyte deformability, explored with whole blood filtration and diffractometric technique, with respect to the group of healthy volunteers.<sup>11</sup>

The erythrocyte deformability is dependent on the surface/volume ratio of the erythrocyte, on internal viscosity related mainly to the concentration of cytosolic calcium, on erythrocyte organic phosphates (ATP and 2.3 DPG), and changes in hemoglobin, and it is also dependent on the dynamic

membrane properties, related to the protein and lipid composition. In addition to allowing the erythrocyte to easily cross microvascular districts of a few microns, so much lower than the geometric characteristics of the red blood cell (RBC), the deformability plays a specific role in the supply to oxygen to tissues.<sup>12</sup>

So far, in patients with acute myocardial infarction (AMI) not divided for age, many are the reports related to the evaluation of this parameter, whose behavior has been described from time to time but almost never full analyzed.<sup>13–18</sup>

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Similarly, there are many reports regarding the RDW in both coronary heart disease and AMI. As is well known, RDW is a measure of the range of variation of the volume of erythrocytes, in terms of percent coefficient of variation. Two factors influencing the change in erythrocyte volume in physiological terms should be considered when assessing this parameter. The first is the variability of bone marrow production that eliminates cells that are not suitable to be circulated through the reticuloendothelial system (ineffective erythropoiesis). The second is related to the progressive aging of circulating erythrocyte population, which is accompanied by a reduction in cell volume due to dehydration; in short, the causes of the increase in RDW lie in 1 of these 4 possibilities: decreased mean volume, increased reticulocyte volume variance, increased heterogeneity in the rate of RBC volume occurring in the peripheral circulation, and delayed RBC clearance.<sup>19</sup> Interest in RDW has waned over the past 2 decades after various and in-depth research have highlighted the close relationship between the increase in RDW and certain cardiovascular diseases, so as to make it consider a predictive marker of a very wide range of cardiovascular disorders. There are many papers about the behavior of RDW in patients with coronary heart disease<sup>20–31</sup> and in AMI patients.<sup>32–37</sup>

We must consider that in AMI especially at the initial stage, there are all the doctrinal assumptions that both the erythrocyte deformability and the RDW are involved in the opposite way. In fact, in the initial or acute phase of the AMI, the erythrocyte deformability is adversely affected by increased lipid peroxidation than from that of protein oxidation that some of us have observed and described in this cohort of patients with juvenile myocardial infarction,<sup>7,8</sup> and the trend of RDW could be associated with the cytokine network that seems to accompany the infarct myocardial event.<sup>38–42</sup> The RDW reflects the increase in cytokines such as IL-6 and TNF- $\alpha$ . These cytokines together with other inflammatory markers alter erythropoiesis and cause a significant variation in erythrocyte maturation.

In this retrospective study on our cohort of patients with juvenile myocardial infarction, we examined the behavior of the 2 parameters at an early stage, 3 and 12 months after the acute event in relation to the main traditional risk factors (smoking habit, family history of coronary artery disease, hypercholesterolemia, arterial hypertension, and diabetes mellitus) and the extent of coronary heart damage, especially evaluating their possible correlation.

## Materials and Methods

### Population

In this study, we examined 119 young subjects (aged <46) with recent AMI, from 2001 to 2007. The time interval between the AMI onset and the investigation was  $13 \pm 7$  days. The diagnosis of AMI was carried out on the basis of clinical picture, electrocardiography, blood parameters (creatinine kinase, troponin, and myoglobin), and echocardiography, according to ESC/ACC/AHA/WHF guidelines.<sup>43</sup> Subjects were admitted either from

the A&E department of our university hospital or were transferred from other hospitals in western Sicily. In each subject, we examined the presence of the main cardiovascular risk factors, including smoking habits, family history of CAD, hypercholesterolemia, arterial hypertension, and diabetes mellitus. Family history consisted of any first-grade relative with clinical manifestation of coronary artery disease at age <55 years. Hypercholesterolemia was defined as a total cholesterol level >220 mg/dL and/or use of lipid-lowering drugs. Diabetes mellitus was defined as a fasting blood glucose level >126 mg/dL and/or the use of hypoglycemic drugs. Arterial hypertension was defined as a systolic blood pressure >140 mm Hg and/or a diastolic blood pressure >90 mmHg and/or the use of antihypertensive drugs. According to the number of cardiovascular risk factors, the young AMI subjects were subdivided into 3 subgroups: 38 of them had 0 to 1 risk factor, 41 had 2 risk factors, and 40 had 3 to 5 risk factors. Coronary angiography was performed only in 101 subjects. In the other cases, the subjects declined their consent or the angiographic evaluation was not carried out because of the long distance between the hospital in which the AMI was diagnosed and the angiographic unit of the university center. The 101 subjects in which coronary angiography was performed were subdivided into 3 groups on the basis of the extent of coronary lesions: 21 subjects did not have any significant coronary lesions, 47 had a single-vessel disease (defined as a stenosis >70% in 1 coronary artery), and 33 had a multivessel disease, which is a stenosis >70% in at least 2 coronary vessels. A revascularization procedure was performed with PCI in 57 patients and with CABG in 8.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital of Palermo. Informed consent was obtained from all subjects involved in the study.

### Methods

In this retrospective study, we evaluated the following parameters: RDW expressed as a percentage and evaluated with the automated blood count; hematocrit (Ht) obtained using an automated hematology analyzer; hemoglobin, expressed in grams per liter and evaluated with the automated blood count; and erythrocyte deformability: to evaluate this hemorheological parameter, a 30  $\mu$ L of anticoagulated blood with 2 mL of dextran solution at a viscosity of 24 mPa was mixed. The measurement was obtained by using the diffractometer Rheodyn SSD of Myrenne, which measures the diffraction pattern of a laser beam passing through erythrocytes suspended in a viscous medium and deformed by a force with defined shear stress. The shear stress employed was 30 and 60 Pa. The erythrocyte deformation was expressed as elongation index (EI) =  $(l - w/l + w) \times 100$ , where  $l$  = length and  $w$  = width of the erythrocytes.

### Statistical Analysis

All statistical analyses were performed using GraphPad Prism version 9.5. The data were expressed as means and standard

deviation. The comparison between the means was effected using the Student *t* test for unpaired data. The comparison between the different subgroups of juvenile AMI according to the traditional cardiovascular risk factors and to the extent of the coronary damage was made employing the 1-way analysis of variance (ANOVA) integrated by the Tukey's test. The comparison between each parameter between initial stage ( $T_1$ ), 3 months ( $T_2$ ), and 12 months ( $T_3$ ) was made using the ANOVA for repeated measures. For the analysis of the different correlations, the Pearson's test was employed. The null hypothesis was evaluated for values of  $P \leq .05$ .

## Results

Preliminary, at the initial phase of this cohort of patients with juvenile AMI, we evaluated means, standard deviation, and range of all parameters considered (Table 1). Immediately

**Table 1.** Means  $\pm$  SD and Ranges of the Erythrocyte Parameters in AMI Patients at  $T_1$ .

AMI $T_1$ ( $n = 119$ )	Mean $\pm$ SD	Range
RDW (%)	13.70 $\pm$ 1.023	11.80-17.00
Ht (%)	44.36 $\pm$ 3.649	35.00-53.00
Hb (g/dL)	14.35 $\pm$ 1.409	9.70-17.90
EI 30 Pa	44.88 $\pm$ 4.14	35.70-56.03
EI 60 Pa	47.91 $\pm$ 4.15	38.87-60.00

Abbreviations: SD, standard deviation; AMI, acute myocardial infarction;  $T_1$ , see text; RDW, red blood cell distribution width; Ht, hematocrit; Hb, hemoglobin; EI 30, elongation index at the shear stress of 30 Pa; EI 60, elongation index at the shear stress of 60 Pa.

afterwards, we compared the behavior of the same parameters in the subgroup of ST-segment elevation myocardial infarction (STEMI) infarcts with that of NSTEMI infarcts. From this comparison, it turns out that in the STEMI subgroup, a reduction in the erythrocyte deformability is evident as EI at 30 and 60 Pa (data not shown).

We then divided, always in the initial phase ( $T_1$ ), the entire cohort into 3 subgroups according to the number of traditional cardiovascular risk factors, observing with the use of the ANOVA, that neither the RDW erythrocyte index nor the erythrocyte deformability, nor the remaining parameters were affected by risk factors (Table 2). The result was similar when, still at an early stage, the entire cohort was divided into 3 subgroups according to the extent of coronary heart damage. Even with this further subdivision, none of the parameter considered seems to have a discriminating role (Table 3). At the initial phase, however, of particular interest is the negative correlation between the RDW erythrocyte index and the EI, both at shear stress of 30 and 60 Pa (Table 4). We then examined the trend of each parameter at 3 and 12 months after the event. The study, this time, concerned only 52 patients who had adhered to the indications formulated at the time of hospital discharge. This evaluation, carried out with the ANOVA for repeated measurements, has shown that among the parameters under examination, only the Ht tends to increase from the initial phase up to 12 months after the infarct event (Table 5). Once again, data relating to the study of correlations between RDW and the remaining parameters are of particular interest both at 3 months ( $T_2$ ) and at 12 months ( $T_3$ ) from the acute event. In fact, both in  $T_2$  and  $T_3$ , there is a negative correlation between RDW and the values of the EI (data not shown).

**Table 2.** Means  $\pm$  SD of the Erythrocyte Parameters in AMI Patients at  $T_1$  Subdivided According to the Number of RFs.

	0-1 RF ( $n = 38$ )	2 RFs ( $n = 41$ )	3-5 RFs ( $n = 40$ )	F
RDW (%)	13.67 $\pm$ 1.071	13.76 $\pm$ 1.051	13.65 $\pm$ 0.968	0.1322
Ht (%)	44.68 $\pm$ 3.313	44.20 $\pm$ 4.155	44.23 $\pm$ 3.468	0.2163
Hb (g/dL)	14.58 $\pm$ 1.250	14.19 $\pm$ 1.549	14.30 $\pm$ 1.406	0.8138
EI 30 Pa	44.33 $\pm$ 4.483	45.05 $\pm$ 3.751	45.24 $\pm$ 4.245	0.5113
EI 60 Pa	47.15 $\pm$ 4.524	48.21 $\pm$ 3.508	48.33 $\pm$ 4.390	0.9402

Abbreviations: SD, standard deviation; AMI, acute myocardial infarction;  $T_1$ , see text; RFs, risk factors; RDW, red blood cell distribution width; Ht, hematocrit; Hb, hemoglobin; EI 30, elongation index at the shear stress of 30 Pa; EI 60, elongation index at the shear stress of 60 Pa.

**Table 3.** Means  $\pm$  SD of the Erythrocyte Parameters in AMI Patients at  $T_1$  Subdivided According to the Number of Stenosed Coronary Vessels.

	No Coronary Stenosis ( $n = 21$ )	1-vessel Disease ( $n = 47$ )	2-3-vessel Disease ( $n = 33$ )	F
RDW (%)	13.59 $\pm$ 1.001	13.70 $\pm$ 1.048	13.30 $\pm$ 1.035	0.2780
Ht (%)	44.48 $\pm$ 3.855	44.15 $\pm$ 3.551	44.82 $\pm$ 3.949	0.3108
Hb (g/dL)	14.08 $\pm$ 1.175	14.32 $\pm$ 1.560	14.56 $\pm$ 1.407	0.7444
EI 30 Pa	45.48 $\pm$ 3.996	44.60 $\pm$ 4.077	44.39 $\pm$ 4.270	0.4825
EI 60 Pa	48.34 $\pm$ 3.903	47.96 $\pm$ 4.201	47.11 $\pm$ 4.111	0.6859

Abbreviations: SD, standard deviation; AMI, acute myocardial infarction;  $T_1$ , see text; RDW, red blood cell distribution width; Ht, hematocrit; Hb, hemoglobin; EI 30, elongation index at the shear stress of 30 Pa; EI 60, elongation index at the shear stress of 60 Pa.

## Discussion

The simultaneous evaluation of RDW and erythrocyte deformability, the latter examined with diffractometric technique, in the cohort of patients with juvenile AMI adds some interesting data to what is already known in this clinical condition.

As is known, the juvenile AMI is between 2% and 10% of all cases of heart attack. Traditional, modifiable, and non-modifiable risk factors must be supplemented by nontraditional risk factors (polycystic ovary, hypoestrogenemia, autoimmune diseases, and inflammatory genetic substrates) and above all the genetic polymorphisms that seem to characterize the cohort of infarcts that are part of the "Sicilian study on juvenile myocardial infarction." About two-thirds of young patients are non-STEMI, but the clinical presentation is not distinguishable from that of older patients. Patients with juvenile AMI have less frequent angina symptoms.<sup>44</sup> In the same patients, it should instead be evaluated the recent use of abuse substances (cocaine and methamphetamine) and, at the same time, always deepen the family history for arterial and venous thrombotic diseases. From 3% to 11% of such young patients may already present with ventricular arrhythmias or sudden cardiac death when the juvenile AMI is traceable to coronary dissection.<sup>45</sup> As for the clinical picture, however, young patients benefit from revascularization and treatment of complications. In the juvenile population, there is often no coronary artery disease or at most only 1 coronary vessel is affected by narrowing; the disease of the 3 vessels is very infrequent. As a result, reperfusion with PCI is more frequent than with CABG and this has a favorable influence on prognosis. In the patients, there is a lower incidence of early or late complications such as cardiac insufficiency, angina, reinfarct, and atrioventricular block. However, it should be stressed as on the prognosis, also in juvenile AMI, may burden a 23% change of developing new cardiovascular

events in the 5-year follow-up" with "In relation to the prognosis, also in juvenile AMI, it could a 23% of possibility of developing new cardiovascular events in the 5-year follow-up."<sup>46</sup>

The preliminary data that emerges from this retrospective study is that the EI, explored to shear stress of 30 and 60 Pa, at the initial phase is reduced in juvenile AMI when compared to the values of the control group ( $P < .05$ ), whereas RDW does not discriminate the 2 groups against the cohort of AMIs subject to the control group. Of particular hemorheological interest is the fact that in the group of infarcted STEMI, EI values are reduced when compared with those found in the non-STEMI group; the RDW does not appear to be discriminating between the 2 subgroups. As previously observed for other parameters of the hemorheological profile, the EI values do not change as the number of cardiovascular factors changes. The same trend was observed for RDW, although there are many reports of its increase in smoking,<sup>47</sup> arterial hypertension,<sup>48–50</sup> lipid profile,<sup>51</sup> metabolic syndrome,<sup>52,53</sup> and diabetic disease.<sup>54,55</sup> With regard to the latter, some authors believe that RDW is an indicator of complications associated with it<sup>56–59</sup> and that it even manages to predict<sup>60</sup> plasma glucose level at 2 h from the start of an oral glucose load curve. As the coronary artery damage strain observed in the course of the coronary artery investigation, as previously verified for other hemorheological determinants, there was no change in the EI values at either 30 or 60 shear stress. Similar is the behavior noted for the RDW that, in fact, does not appear to vary in the 3 considered subgroups. These last data however do not seem to align with what was described by other authors,<sup>61,62</sup> which have shown an increase in RDW with varying severity and complexity of coronary heart disease and also the number of coronaries involved. By other authors, it is reiterated, through a follow-up carried out up to 3 years after the acute event, that in infarcted patients, not subdivided by age, the increase in RDW appears to be a marker of adverse clinical events and cardiovascular, both intra-hospital and long-term mortality.<sup>63,64</sup>

Data of particular doctrinal interest is what is recorded when the correlation between the RDW and EI values at 30 and 60 shear stress has been evaluated. In the entire cohort of patients with juvenile AMI, the negative correlation between these 2 parameters is evident. From the point of view of clinical hemorheology, it makes seriously reflect in how much it is not to exclude that in the determinism of the deformability of the

**Table 4.** Correlations Between RDW and the Other Erythrocyte Parameters in AMI Patients at  $T_1$ .

RDW versus	Ht	Hb	EI 30 Pa	EI 60 Pa
<i>r</i>	0.0370	−0.1627	−0.2221	−0.1885
<i>P</i>	.689	.077	.015	.040

Abbreviations: AMI, acute myocardial infarction;  $T_1$ , see text; RDW, red blood cell distribution width; Ht, hematocrit; Hb, hemoglobin; EI 30, elongation index at the shear stress of 30 Pa; EI 60, elongation index at the shear stress of 60 Pa.

**Table 5.** Means  $\pm$  SD of the Erythrocyte Parameters in AMI Patients Who Completed the Follow-Up ( $n = 52$ ).

	$T_1$	$T_2$	$T_3$	<i>F</i>
RDW (%)	13.55 $\pm$ 0.968	13.88 $\pm$ 0.920	13.66 $\pm$ 0.8384	2.765
Ht (%)	43.79 $\pm$ 3.696	44.75 $\pm$ 3.704	45.04 $\pm$ 3.689*	4.531**
Hb (g/dL)	14.25 $\pm$ 1.554	14.48 $\pm$ 1.412	14.59 $\pm$ 1.342	2.563
EI 30 Pa	44.67 $\pm$ 3.755	44.65 $\pm$ 4.584	43.97 $\pm$ 4.309	1.067
EI 60 Pa	47.74 $\pm$ 4.027	47.71 $\pm$ 4.211	47.46 $\pm$ 4.279	0.156

Abbreviations: SD, standard deviation; AMI, acute myocardial infarction;  $T_1$ ,  $T_2$ ,  $T_3$ , see text; RDW, red blood cell distribution width; Ht, hematocrit; Hb, hemoglobin; EI 30, elongation index at the shear stress of 30 Pa; EI 60, elongation index at the shear stress of 60 Pa.

\* $P < .05$  versus  $T_1$  (Tukey's test)

\*\* $P < .05$  (repeated measurements ANOVA)

RBCs must be taken in due consideration the degree of anisocytosis that of fact is that which is expressed by RDW. Until now, the data obtained in relation to the study of correlation between these 2 parameters have not converged in the literature. The first response concerned a cohort of 293 adults with an average age of  $71.1 \pm 13.3$  participating in a longitudinal aging study in which a significant negative correlation was found between the RDW and the EI evaluated at shear stress of 3 Pa.<sup>65</sup> This correlation became significantly more marked when the entire cohort excluded the group of anemic subjects. Other authors instead both in hypertensive patients,<sup>66</sup> and in patients with AMI<sup>67</sup> both in subjects with metabolic diseases<sup>68</sup> showed a positive correlation between these 2 parameters. Similar to what Patel found, a negative correlation between RDW and EI occurred both in subjects with thalassemic trait and in patients with hematological neoplasms.<sup>69</sup>

The behavior of the EI values, RDW, and the remaining parameters in the following months ( $T_2$  and  $T_3$ ) from the acute event does not seem to undergo significant changes. What happens to EI values does not surprise us since in all our previous reports<sup>70</sup> concerning the hemorheological profile related to the entire cohort of patients with juvenile AMI, the variations regarding blood viscosity, plasma, and serum viscosity and whole blood filtration were never detected not only at 3 months ( $T_2$ ) but also at 12 months ( $T_3$ ) from the acute event, and this is in agreement with what is now observed and seems to reiterate the peculiarity of the patients who are part of the Sicilian study on juvenile AMI that seem to be characterized by the high percentage of proinflammatory genetic polymorphisms.

The last consideration that concerns the data of this study is regarding what happens several months after the infarct event relative to the persistent negative correlation between RDW and EI values. So not only in the initial phase but also after 3 and 12 months, when you have certainly changed both the cytokine network that partly lipid peroxidation and protein oxidation, which confirms the interdependence related to these 2 parameters.

## Conclusions

The data obtained in this report regarding the cohort of patients enrolled in this Sicilian study on juvenile AMI show that only the erythrocyte deformability expressed as EI to shear stress of 30 and 60 Pa is reduced at the initial phase, when compared to that of the control group, and that only this determinant is able to distinguish between STEMI and non-STEMI infarctions, with a negative correlation with the RDW. Erythrocyte deformability, as already established for other hemorheological determinants, does not seem to change with the passing of months and, even after 3 and 12 months from the acute event, correlates significantly with RDW.

As a limitation, this is a retrospective analysis, but this does not reduce the value of the obtained data.

## Author Contributions

GC conceptualized the study, analyzed and interpreted the data, and wrote the original draft; MC performed writing—review and editing; RLP performed statistical analysis; MM performed laboratory

testing; EC visualized the study. All authors read and approved the final manuscript.


## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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## References

1. Caimi G, Hoffmann E, Montana M, et al. Haemorheological pattern in young adults with acute myocardial infarction. *Clin Hemorheol Microcirc.* 2003;29(1):11-18.
2. Caimi G, Hoffmann E, Canino B, et al. Polymorphonuclear leukocyte membrane fluidity and cytosolic Ca(2+) content in young adults with acute myocardial infarction. Evaluation at the initial stage and after 12 months. *Clin Hemorheol Microcirc.* 2004;31(1):41-47.
3. Lo Presti R, Tozzi Ciancarelli MG, Canino B, et al. Polymorphonuclear leukocyte membrane fluidity and cytosolic Ca2 + concentration in subjects with vascular atherosclerotic disease subdivided according to its extent. *Clin Hemorheol Microcirc.* 2006; 35(1-2):199-201.
4. Lo Presti R, D'Amico T, Montana M, Canino B, Romano A, Caimi G. Platelet activation markers in long-term follow-up of young subjects with acute myocardial infarction. *Clin Hemorheol Microcirc.* 2006;35(4):527-528.
5. Caimi G, Hoffmann E, Montana M, Incalcaterra E, Canino B, Lo Presti R. Beta-thromboglobulin and platelet factor 4 in juvenile myocardial infarction. *Clin Appl Thromb Hemost.* 2007;13(1):108-109.
6. Incalcaterra E, Caruso M, Balistreri CR, et al. Role of genetic polymorphisms in myocardial infarction at young age. *Clin Hemorheol Microcirc.* 2010;46(4):291-298.
7. Lo Presti R, Catania A, D'Amico T, Montana M, Caruso M, Caimi G. Oxidative stress in young subjects with acute myocardial infarction: Evaluation at the initial stage and after 12 months. *Clin Appl Thromb Hemost.* 2008;14(4):421-427.
8. Caimi G, Canino B, Incalcaterra E, Ferrera E, Montana M, Lo Presti R. Behaviour of protein carbonyl groups in juvenile myocardial infarction. *Clin Hemorheol Microcirc.* 2013;53(4):297-302.
9. Caimi G, Lo Presti R, Canino B, Ferrera E, Hopps E. Behaviour of the neutrophil to lymphocyte ratio in young subjects with acute myocardial infarction. *Clin Hemorheol Microcirc.* 2016;62(3):239-247.
10. Caimi G, Lo Presti R, Andolina G, Hopps E. Short-term prognosis of juvenile myocardial infarction: Role of plasma viscosity. *Angiology.* 2016;67(9):799-801.
11. Caimi G, Valenti A, Lo Presti R. Acute myocardial infarction in young adults: Evaluation of the haemorheological pattern at the initial stage, after 3 and 12 months. *Ann Ist Super Sanita.* 2007;43(2): 139-143.

12. Benedik PS, Hamlin SK. The physiologic role of erythrocytes in oxygen delivery and implications for blood storage. *Crit Care Nurs Clin North Am.* 2014;26(3):325-335.
13. Dodds AJ, Boyd MJ, Allen J, Bennett ED, Flute PT, Dormandy JA. Changes in red cell deformability and other haemorrhological variables after myocardial infarction. *Br Heart J.* 1980;44(5):508-511.
14. Sargento L, Monteiro J, Saldanha C, Perdigão C, Martins e Silva J, Ribeiro C. Avaliação da deformabilidade eritrocitária em doentes com enfarte agudo do miocárdio por meio de ectacitometria laser [The evaluation of erythrocyte deformability in patients with an acute myocardial infarct by means of laser ectacytometry]. *Rev Port Cardiol.* 1996;15(12):935-936. Portuguese.
15. Penco M, Romano S, Dagianti A Jr, Tozzi-Ciancarelli MG, Dagianti A. Modifications of whole blood filterability during acute myocardial infarction. *Clin Hemorheol Microcirc.* 2000;22(2):153-159.
16. Wasilewski J, Turczyński B, Słowińska L, Kowalik V, Osadnik T, Poloński L. Haemorheological factors and myocardial reperfusion in patients with ST-elevation myocardial infarction undergoing primary coronary intervention. *Kardiol Pol.* 2007;65(7):778-785. ; discussion 786-7.
17. Zorio E, Murado J, Arizo D, et al. Haemorheological parameters in young patients with acute myocardial infarction. *Clin Hemorheol Microcirc.* 2008;39(1-4):33-41.
18. Park KH, Kim U, Choi KU, et al. Hemorheologic alterations in patients with type 2 diabetes mellitus presented with an acute myocardial infarction. *Diabetes Metab J.* 2018;42(2):155-163. Erratum in: *Diabetes Metab J.* 2018 Jun;42(3):254.
19. Patel HH, Patel HR, Higgins JM. Modulation of red blood cell population dynamics is a fundamental homeostatic response to disease. *Am J Hematol.* 2015;90(5):422-428.
20. Tonelli M, Sacks F, Arnold M, et al. for the Cholesterol and Recurrent Events (CARE) trial investigators. Relation between red blood cell distribution width and cardiovascular event rate in people with coronary disease. *Circulation.* 2008;117(2):163-168.
21. Isik T, Kurt M, Ayhan E, et al. Relation of red cell distribution width with presence and severity of coronary artery ectasia. *Clin Appl Thromb Hemost.* 2012;18(5):441-447.
22. Tziakas D, Chalikias G, Grapsa A, Gioka T, Tentis I, Konstantinides S. Red blood cell distribution width: A strong prognostic marker in cardiovascular disease: Is associated with cholesterol content of erythrocyte membrane. *Clin Hemorheol Microcirc.* 2012;51(4):243-254.
23. Ma FL, Li S, Li XL, et al. Correlation of red cell distribution width with the severity of coronary artery disease: A large Chinese cohort study from a single center. *Chin Med J (Engl).* 2013;126(6):1053-1057.
24. Bujak K, Wasilewski J, Osadnik T, et al. The prognostic role of red blood cell distribution width in coronary artery disease: A review of the pathophysiology. *Dis Markers.* 2015;2015:824624. Epub 2015 Aug 26.
25. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: A simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci.* 2015;52(2):86-105.
26. Nagula P, Karumuri S, Otikunta AN, Yerrabandi SRV. Correlation of red blood cell distribution width with the severity of coronary artery disease—A single center study. *Indian Heart J.* 2017;69(6):757-761.
27. Li N, Zhou H, Tang Q. Red blood cell distribution width: A novel predictive indicator for cardiovascular and cerebrovascular diseases. *Dis Markers.* 2017;2017:7089493.
28. Avci E, Kiris T, Demirtas AO, Kadi H. Relationship between high-density lipoprotein cholesterol and the red cell distribution width in patients with coronary artery disease. *Lipids Health Dis.* 2018;17(1):53.
29. Arkew M, Gemechu K, Haile K, Asmerom H. Red blood cell distribution width as novel biomarker in cardiovascular diseases: A literature review. *J Blood Med.* 2022;13(Aug 2):413-424.
30. Katamreddy A, Kokkinidis DG, Miles J, Siasos G, Giannakoulas G, Faillace RT. Elevated red cell distribution width and cardiovascular mortality in ASCVD risk cohorts: National Health and Nutrition Examination Survey (NHANES III). *Rev Cardiovasc Med.* 2022;23(2):51.
31. Xiao Q, Yan D, Qin J, et al. Dynamic changes in red cell distribution width can predict major adverse cardiovascular events after PCI in patients with unstable angina pectoris: A retrospective cohort study. *Dis Markers.* 2022;2022(Jun 8):2735717.
32. Dabbah S, Hammerman H, Markiewicz W, Aronson D. Relation between red cell distribution width and clinical outcomes after acute myocardial infarction. *Am J Cardiol.* 2010;105(3):312-317.
33. Sun XP, Chen WM, Sun ZJ, et al. Impact of red blood cell distribution width on long-term mortality in patients with ST-elevation myocardial infarction. *Cardiology.* 2014;128(4):343-348.
34. Skjelbakken T, Lappégard J, Ellingsen TS, et al. Red cell distribution width is associated with incident myocardial infarction in a general population: The Tromsø Study. *J Am Heart Assoc.* 2014;3(4):e001109.
35. Sahin O, Akpek M, Sarli B, et al. Association of red blood cell distribution width levels with severity of coronary artery disease in patients with non-ST elevation myocardial infarction. *Med Princ Pract.* 2015;24(2):178-183.
36. Lappégard J, Ellingsen TS, Hindberg K, et al. Impact of chronic inflammation, assessed by hs-CRP, on the association between red cell distribution width and arterial cardiovascular disease: The Tromsø Study. *TH Open.* 2018;2(2):e182-e189.
37. Huang S, Zhou Q, Guo N, et al. Association between red blood cell distribution width and in-hospital mortality in acute myocardial infarction. *Medicine (Baltimore).* 2021;100(15):e25404.
38. Halawa B, Salomon P, Jolda-Mydłowska B, Zyśko D. Stezenia czynnika martwicy nowotworów (TNF-alpha) i interleukiny 6 (IL-6) w surowicy chorych na świeży zawał mięśnia serca [Levels of tumor necrosis factor (TNF-alpha) and interleukin 6 (IL-6) in serum of patients with acute myocardial infarction]. *Pol Arch Med Wewn.* 1999;101(3):197-203. Polish.
39. Valgimigli M, Ceconi C, Malagutti P, et al. Tumor necrosis factor-alpha receptor 1 is a major predictor of mortality and new-onset heart failure in patients with acute myocardial infarction: The cytokine-activation and long-term prognosis in myocardial infarction (C-ALPHA) study. *Circulation.* 2005;111(7):863-870.
40. Neri M, Fineschi V, Di Paolo M, et al. Cardiac oxidative stress and inflammatory cytokines response after myocardial infarction. *Curr Vasc Pharmacol.* 2015;13(1):26-36.
41. Hartman MHT, Groot HE, Leach IM, Karper JC, van der Harst P. Translational overview of cytokine inhibition in acute myocardial

- infarction and chronic heart failure. *Trends Cardiovasc Med*. 2018;28(6):369-379.
42. Mitsis A, Kadoglou NPE, Lambadiari V, et al. Prognostic role of inflammatory cytokines and novel adipokines in acute myocardial infarction: An updated and comprehensive review. *Cytokine*. 2022;153(May):155848.
  43. Thygesen K, Alpert JS, Jaffe AS, et al. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth universal definition of myocardial infarction (2018). *Circulation*. 2018;138(20):e618-e651. Erratum in: *Circulation*. 2018 Nov 13;138(20):e652.
  44. Doughty M, Mehta R, Bruckman D, et al. Acute myocardial infarction in the young—the University of Michigan experience. *Am Heart J*. 2002;143(1):56-62.
  45. Hayes SN, Kim ESH, Saw J, et al. American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke Council. Spontaneous coronary artery dissection: Current state of the science: A scientific statement from the American Heart Association. *Circulation*. 2018;137(19):e523-e557.
  46. Fornengo C, Anselmino M, Iacovino C, Palumbo L, Trevi GP, Bergerone S. Five year prognosis of an Italian cohort of juvenile acute myocardial infarction patients. *Minerva Cardioangiol*. 2010;58(4):433-439.
  47. Kurtoglu E, Aktürk E, Korkmaz H, et al. Elevated red blood cell distribution width in healthy smokers. *Turk Kardiyol Dern Ars*. 2013;41(3):199-206.
  48. Gunebakmaz O, Kaya MG, Duran M, Akpek M, Elcik D, Eryol NK. Red blood cell distribution width in 'non-dippers' versus 'dippers'. *Cardiology*. 2012;123(3):154-159.
  49. Tanindi A, Topal FE, Topal F, Celik B. Red cell distribution width in patients with prehypertension and hypertension. *Blood Press*. 2012;21(3):177-181.
  50. Ozcan F, Turak O, Durak A, et al. Red cell distribution width and inflammation in patients with non-dipper hypertension. *Blood Press*. 2013;22(2):80-85.
  51. Lippi G, Sanchis-Gomar F, Danese E, Montagnana M. Association of red blood cell distribution width with plasma lipids in a general population of unselected outpatients. *Kardiol Pol*. 2013;71(9):931-936.
  52. Laufer Perl M, Havakuk O, Finkelstein A, et al. High red blood cell distribution width is associated with the metabolic syndrome. *Clin Hemorheol Microcirc*. 2015;63(1):35-43.
  53. Ren D, Wang J, Li H, Li Y, Li Z. Red blood cell distribution width and carotid intima-media thickness in patients with metabolic syndrome. *BMC Cardiovasc Disord*. 2017;17(1):44.
  54. Veeranna V, Zalawadiya SK, Panaich SS, Ramesh K, Afonso L. The association of red cell distribution width with glycated hemoglobin among healthy adults without diabetes mellitus. *Cardiology*. 2012;122(2):129-132.
  55. Wang J, Zhang Y, Wan Y, Fan Z, Xu R. The relationship between red blood cell distribution width and incident diabetes in Chinese adults: A cohort study. *J Diabetes Res*. 2020;2020(Feb 27):1623247.
  56. Malandrino N, Wu WC, Taveira TH, Whitlatch HB, Smith RJ. Association between red blood cell distribution width and macrovascular and microvascular complications in diabetes. *Diabetologia*. 2012;55(1):226-235.
  57. Afonso L, Zalawadiya SK, Veeranna V, Panaich SS, Niraj A, Jacob S. Relationship between red cell distribution width and microalbuminuria: A population-based study of multiethnic representative US adults. *Nephron Clin Pract*. 2011;119(4):c277-c282.
  58. Wang ZS, Song ZC, Bai JH, et al. Red blood cell count as an indicator of microvascular complications in Chinese patients with type 2 diabetes mellitus. *Vasc Health Risk Manag*. 2013;9:237-243.
  59. Magri CJ, Fava S. Red blood cell distribution width and diabetes-associated complications. *Diabetes Metab Syndr*. 2014;8(1):13-17.
  60. Tripolino C, Irace C, Carallo C, De Franceschi MS, Scavelli FB, Gnasso A. Red blood cell distribution width predicts two-hours plasma glucose levels during OGTT. *Clin Hemorheol Microcirc*. 2016;62(1):63-69.
  61. Bekler A, Gazi E, Tenekecioglu E, et al. Assessment of the relationship between red cell distribution width and fragmented QRS in patients with non-ST elevated acute coronary syndrome. *Med Sci Monit*. 2014;20(Feb 27):413-419.
  62. Balta S, Demirkol S, Aparci M, Arslan Z, Ozturk C. Red cell distribution width in myocardial infarction. *Med Princ Pract*. 2015;24(6):584.
  63. Uyarel H, Ergelen M, Cicek G, et al. Red cell distribution width as a novel prognostic marker in patients undergoing primary angioplasty for acute myocardial infarction. *Coron Artery Dis*. 2011;22(3):138-144.
  64. Gul M, Uyarel H, Ergelen M, et al. The relationship between red blood cell distribution width and the clinical outcomes in non-ST elevation myocardial infarction and unstable angina pectoris: A 3-year follow-up. *Coron Artery Dis*. 2012;23(5):330-336.
  65. Patel KV, Mohanty JG, Kanapuru B, Hesdorffer C, Ershler WB, Rifkind JM. Association of the red cell distribution width with red blood cell deformability. *Adv Exp Med Biol*. 2013;765:211-216.
  66. Fornal M, Wizner B, Cwynar M, et al. Association of red blood cell distribution width, inflammation markers and morphological as well as rheological erythrocyte parameters with target organ damage in hypertension. *Clin Hemorheol Microcirc*. 2014;56(4):325-335.
  67. Vayá A, Rivera L, de la Espriella R, et al. Red blood cell distribution width and erythrocyte deformability in patients with acute myocardial infarction. *Clin Hemorheol Microcirc*. 2015;59(2):107-114.
  68. Vayá A, Alis R, Suescún M, et al. Association of erythrocyte deformability with red blood cell distribution width in metabolic diseases and thalassemia trait. *Clin Hemorheol Microcirc*. 2015;61(3):407-415.
  69. Lee JM, Suh JS, Kim YK. Red blood cell deformability and distribution width in patients with hematologic neoplasms. *Clin Lab*. 2022;68(10):2118-2124.
  70. Caimi G, Hopps E, Montana M, et al. Analysis of the blood viscosity behavior in the Sicilian study on juvenile myocardial infarction. *Clin Appl Thromb Hemost*. 2018;24(8):1276-1281.