sciendo

J Med Biochem 2019; 38 (4) DOI: 10.2478/jomb-2018-0047

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 38: 468–474, 2019

Original paper
Originalni naučni rad

RED BLOOD CELL DISTRIBUTION WIDTH PREDICTS 1-MONTH COMPLICATIONS AFTER PERCUTANEOUS TRANSLUMINAL ANGIOPLASTY

ŠIRINA DISTRIBUCIJE ERITROCITA PREDVIĐA 1-MESEČNE KOMPLIKACIJE POSLE PERKUTANE TRANSLUMINALNE ANGIOPLASTIJE

Gian Franco Veraldi[1], Luca Mezzetto[1], Lorenzo Scorsone[1], Marco Macrì[1], Fabio Simoncini[1], Giuseppe Lippi[2]

[1]Department of Vascular Surgery, University of Verona-School of Medicine, University Hospital of Verona, Verona, Italy
[2]Section of Clinical Biochemistry, University of Verona, Verona, Italy

Summary

Background: The identification of patients at higher risk of developing percutaneous transluminal angioplasty (PTA)-related complications is pivotal for achieving better clinical outcomes. We carried out a single-center, observational, retrospective study to explore whether in-hospital changes of red blood cell distribution width (RDW) may help predicting early development of PTA-related complications.
Methods: The study population consisted of all consecutive patients who underwent PTA for severe peripheral artery occlusive disease (PAOD) during a 2-year period. RDW was measured at hospital admission and discharge, and the delta was calculated. Patient follow-up was routinely performed 1-month after hospital discharge, and was based on thoughtful medical assessment and arterial ultrasonography. The control population consisted of 352 ostensibly healthy subjects.
Results: The final PTA group consisted of 224 patients. Hemoglobin was lower, whilst mean corpuscular volume (MCV) and RDW were higher in PAOD cases than in controls. Overall, 11 PAOD patients (4.9%) developed clinically significant PTA-related complications 1-month after hospital discharge. Patients who developed 1-month PTA-related complications had lower hemoglobin concentration, but higher RDW and delta RDW than those who did not. Patients with delta RDW >1 had 60% higher risk

Kratak sadržaj

Uvod: Identifikacija pacijenta sa povećanim rizikom od razvoja perkutane transluminalne angioplastije (PTS)-povezane sa komplikacijama je u osnovi za postizanje boljeg kliničkog ishoda. Izvođena je jedno-centrična, opservaciona, retrospektivna studija kako bi se istražilo da li u hospitalnim uslovima promene širine distribucije eritrocita (RDW) mogu pomoći predviđanju ranog razvoja PTA-povezanih komplikacija.
oštećenja (ADHF).
Metode: Ispitivana grupa se sastojala od pacijenata koji su imali PTA usled teškog perifernog okluzivnog oboljenja (PAOD) u toku dvogodišnjeg perioda. RDW je meren pri prijemu u bolnicu i nakon otpuštanja, nakon čega je izračunata delta vrednost. Pacijenti su rutinski praćeni mesec dana nakon otpuštanja iz bolnice, medicinski procenjivani i urađena im je arterijska ultrasonografija. Kontrolna grupa se sastojala od 352 zdrave osobe.
Rezultati: Krajnja PTA grupa imala je 224 pacijenta. Hemoglobin je bio snižen, dok su MCV i RDW bili viši u slučaju PAOD u odnosu na kontrolnu grupu. Ukupno gledajući, 11 PAOD pacijenata (4,9%) razvilo je kliničke znake značajnih PTA komplikacija 1 mesec nakon otpuštanja iz bolnice. Ovi pacijenti su imali snižene koncentracije hemoglobina, povišene vrednosti RDW i delta RDW u odnosu na one koji to nisu imali. Pacijenti sa delta RDW > 1 imali su 60% viši rizik za razvoj jednomesečnih komplikacija i 88% veći rizik za

Address for correspondence:

Prof. Giuseppe Lippi
Section of Clinical Biochemistry
University Hospital of Verona
Piazzale LA Scuro, 37134 – Verona, Italy
e-mail: giuseppe.lippi@univr.it

of developing 1-month PTA-related complications and 88% higher risk of developing early reocclusion. Overall, RDW exhibited an area under the curve (AUC) of 0.68 and 0.74 for predicting 1-month PTA-related complications and early reocclusion, respectively.
Conclusions: The results of this study suggest that RDW may play a role for guiding the clinical decision making of PTA patients immediately after hospital discharge.

Keywords: peripheral artery occlusive disease, percutaneous transluminal angioplasty, complications, restenosis, red blood cell distribution width

razvoj okluzije. Ukupno gledajući, RDW je imala površinu ispod krive (AUC) 0,68 i 0,74 za predviđanje 1-mesečnih PTA-srodnih komplikacija, odnosno za ranu reokluziju.
Zaključak: Rezultati ovog izučavanja ukazuju da RDW može imati značaj za donošenje kliničke odluke da se PTA pacijenti prate odmah nakon otpuštanja iz bolnice.

Ključne reči: periferna arterijska okluzija, perkutana transluminalna angioplastija, komplikacije, restenoza, širina distribucije eritrocita

Introduction

Peripheral artery occlusive disease (PAOD), also known as peripheral artery disease (PAD), is a rather frequent pathology, affecting as many as 13% subjects aged 50 years or older in Western Countries (1). Atherosclerosis is the leading underlying mechanism causing PAOD, wherein stenosis or occlusion of peripheral arteries due to the presence of large atherosclerotic plaques reduce blood flow up to critical ischemia and tissue necrosis in the affected limb. Albeit individuals with PAOD may remain asymptomatic for long, between 5–25% patients will manifest an array of worsening signs and symptoms (i.e., claudication, pallor, rest pain, paraesthesia, paralysis, up to ulceration and gangrene), which may then require elective or urgent revascularization by endovascular or surgical techniques. In these patients, the 5-year risks of amputation and all-cause mortality are as high as 3% and 20%, respectively and, independently of the selected approach for revascularization, clinical results remain largely debated (2). Therefore, other variables need to be investigated for better predicting the risk of re-vascularization failure.

Besides clinical history and examination (i.e., ankle-brachial index), the diagnosis of PAOD is essentially based on duplex ultrasonography, which allows to accurately identifying and localizing atherosclerotic plaques, as well as assessing their size and severity by means of velocity criteria (3). Due to the high burden of disability and mortality of PAOD, the recent guidelines of the European Society of Cardiology (ESC) strongly recommend that patients should receive an appropriate medical therapy (mostly based on antihypertensive, antiplatelet or anticoagulant drugs), combined with a healthy lifestyle (i.e., physical activity, smoking cessation, weight loss, and so forth) (3). In patients who will not benefit from medical or exercise therapy, as well as in those presenting with impairment of daily life activities or limb-threatening ischemia, percutaneous transluminal angioplasty (PTA) is the recommended therapeutic option, since this treatment has been shown to enhance limb salvage and reduce the risk of both disability and death (3). Albeit a number of complications, especially reocclusion, hematomas, arteriovenous fistulae, pseudoaneurysms and infections, may occur in more than half of patients within 1 year after PTA (4, 5), some patients may also develop early acute complications and restenosis (i.e., within 1 to 3 months), which would hence require a timely, often urgent, endovascular management (6).

The identification of patients at higher risk of developing restenosis and other PTA-related complications seems hence crucial for achieving better clinical (i.e., improving patient outcome) and economic (i.e., reducing hospital readmission and management) benefits. Notably, some demographic (i.e., age, sex), laboratory (i.e., C reactive protein, lipoprotein[a], homocysteine), lesion and procedural risk factors have been identified and used during the last decades, but none of these was found to have an optimal diagnostic efficiency for predicting short- and long-term risk of PTA-related complications or reocclusion in large prospective studies (5). On the other hand, Lee et al recently showed that in-hospital increase of red blood cell distribution width (RDW) value, which reliably mirrors an escalating impairment of erythrocyte biology and anisocytosis, was a significant predictor of early adverse events after coronary artery by-pass grafting (CABG) (7). Therefore, we carried out a single-center, observational, retrospective study to explore whether in-hospital changes of RDW values may also help predicting the early development of PTA-related complications and restenosis after hospital discharge.

Materials and Methods

The study population consisted of all consecutive patients who underwent PTA for severe PAOD at the University Hospital of Verona (Verona, Italy) between April 2016 and April 2018. PAOD was diagnosed by physical examination and ultrasound as first, and was then confirmed by lower extremities Computer Tomography (CT-scan) with iodine-contrast or Magnetic Resonance (MR) with gadoline-contrast. Results of hematological testing were retrospectively collected for all patients upon hospital admission and discharge after PTA. Revascularization was performed

according to local practice, by PTA first, eventually followed by bare-metal stent placement in patients with unsatisfactory angiographic results. According to local clinical practice, patient follow-up was routinely performed 1-month after hospital discharge, and was based on thoughtful medical assessment, laboratory testing and arterial ultrasonography. The mean time of hospital admission was 1 day. The primary endpoint was the development of PTA-related complications, thus including reocclusion, hematomas, infections and death. The control population consisted of all ostensibly healthy subjects who underwent routine medical check-up (including laboratory testing) during the same period (i.e., between April 2016 and April 2018).

All hematological parameters, thus including hemoglobin, mean corpuscular volume (MCV) and RDW were always measured using the same analyzers (Sysmex XN, Sysmex Inc., Kobe, Japan). The local laboratory is certified according to the ISO 15189: 2012 standard, and the quality of data has been validated throughout the study period by regular performance of internal quality control (IQC) procedures and participation to an External Quality Assessment (EQA) scheme. The delta RDW was calculated as the ratio between the RDW value measured upon hospital discharge and admission (i.e., [discharge RDW]/[admission RDW]). Significance of differences among groups were assessed with Mann-Whitney (for continuous variables) or Chi-square (for categorical variables) tests. The diagnostic performance was finally evaluated using Receiver Operating Characteristics (ROC) curve analysis. The statistical analysis was performed with Analyse-it (Analyse-it Software Ltd, Leeds, UK) and MedCalc Version 12.3.0 (MedCalc Software, Mariakerke, Belgium). Statistical significance was set at $p<0.05$. This retrospective observational study used anonymized patients' data and was carried out in accordance with the Declaration of Helsinki, under the terms of relevant local legislation, and was cleared by the Institutional Review Board. The requirement for informed consent was waived due to the observational, retrospective nature of this study.

Results

The final study population consisted of 242 consecutive patients who underwent PTA and 352 ostensibly healthy subjects. No PTA patients were lost on follow-up, but 18 of these patients ought to be excluded from our retrospective analysis since hematological testing was not performed at hospital discharge, so that the final PTA group consisted of 224 patients. The demographic and laboratory data of controls and PTA patients at hospital admission is shown in *Table I*. The age and the sex distributions were found to be similar between groups, whilst a significant difference was found for values of hemoglobin (lower in PTA cases), MCV (higher in PTA cases) and RDW (higher in PTA cases). In multivariate analysis, hemoglobin (β coefficient, 0.01; 95% CI, 0–0.01; $p<0.001$), MCV (β coefficient, 0.01; 95% CI, 0.01–0.02; $p<0.001$) and RDW (β coefficient, 0.08; 95% CI, 0.06–0.10; $p<0.001$) were confirmed to be significant predictors of PAOD.

Table I Comparison of demographic and laboratory data between percutaneous transluminal angioplasty (PTA) cases and controls. Results are shown and median and interquartile range or proportion.

Parameter	Controls	PTA patients	p
n	352	224	–
Age (years)	73 (12)	74 (12)	0.107
Sex (F/M)	115/237	72/152	0.484
Hemoglobin (g/L)	135 (62)	131 (28)	<0.001
MCV (fL)	89 (10)	93 (7)	<0.001
RDW (%)	13.7 (2.1)	14.3 (2.2)	<0.001

MCV, mean corpuscular volume; PTA, percutaneous transluminal angioplasty; RDW, red blood cell distribution width

In agreement with previous findings (8), 1-month after hospital discharge a total number of 11 patients (4.9%) developed clinically significant PTA-related complications, including restenosis needing urgent re-intervention (n=7), major hematomas at site of PTA (n=3) and severe infection with toe necrosis (n=1). One of the patient who developed hematoma (severe retroperitoneal hematoma, then followed by infection and sepsis) died during hospital readmission. The demographic and laboratory data of PTA patients, clustered according to presence or absence of 1-month PTA-related complications after hospital discharge, is shown in *Table II*. Interestingly, no significant differences could be observed for age, sex and type of medical treatment between patients who developed PTA-related complications and those who did not. No significant difference could also be noticed between admission or discharge values of hemoglobin ($p=0.365$), MCV ($p=0.487$) and RDW ($p=0.267$) in patients with or without 1-month PTA-related complications, whilst in patients who developed 1-month PTA-related complications the hemoglobin concentration was marginally lower ($p=0.041$) and the RDW value was significantly higher ($p=0.013$). Even more importantly, the delta RDW was marginally but significantly higher in patients who developed PTA-related complications compared to those who did not (1.03 versus 1.00; $p=0.041$), and the number of patients with delta RDW value >1 (i.e., increased RDW at discharge compared with the admission value) was nearly

Table II Comparison of demographic and laboratory data percutaneous transluminal angioplasty (PTA) patients with or without complications 1 at 1 month after hospital discharge. Results are shown as median and interquartile range or proportions.

Parameter	No complications	P admission vs discharge	Complications	P admission vs discharge	P complications vs no complications
n	213	–	11	–	–
Age (years)	74 (13)	–	72 (15)	-	0.135
Sex (F/M)	66/147	–	5/6	–	0.051
Discharge therapy (APT/OAC)	173/40		8/3		0.486
Hemoglobin (g/L)					
- Admission value	130 (27)	0.365	137 (54)	0.041	0.283
- Discharge value	125 (29)		121 (46)		0.334
MCV (fL)					
– Admission value	93 (7)	0.487	95 (9)	0.074	0.427
– Discharge value	92 (9)		91 (10)		0.358
RDW (%)					
– Admission value	14.3 (2.2)	0.267	13.2 (1.4)	0.013	0.149
– Discharge value	14.3 (2.0)		14.1 (1.7)		0.333
– Delta RDW	1.00 (0.06)	–	1.03 (0.04)	–	0.041
– Delta RDW >1 (n)	97/213	–	8/11	–	0.039

APT, antiplatelet therapy; MCV, mean corpuscular volume; OAC, oral anticoagulants, PTA, percutaneous transluminal angioplasty; RDW, red blood cell distribution width

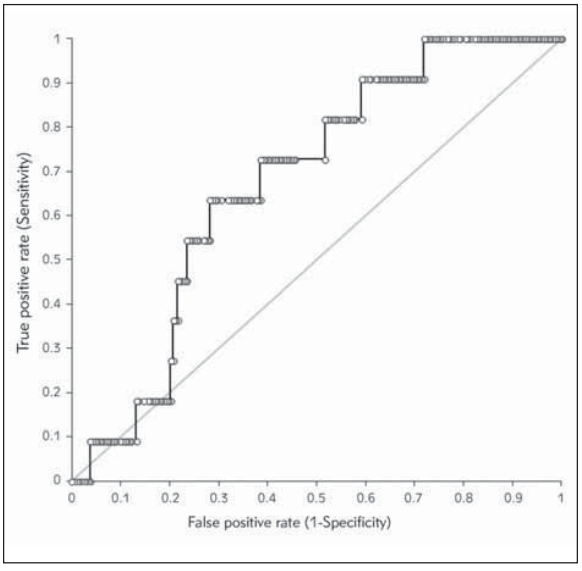

Figure 1 Diagnostic performance (Receiver Operating Characteristics curve) of delta red blood cell distribution width (RDW) for predicting 1-month complications after percutaneous transluminal angioplasty (PTA).

double in the latter group (73% versus 46%; p=0.039) (*Table II*). Conversely, both the admission and discharge values of hemoglobin, MCV and RDW did not differ between patients who developed 1-month PTA-related complications and those who did not. Patients with delta RDW >1 had 60% higher risk of developing 1-month PTA-related complications after hospital discharge (relative risk [RR], 1.60; 95% confidence interval [95% CI], 1.08–2.36; p=0.019), and 88% higher risk of developing early reocclusion (RR, 1.88; 95% CI, 1.34–2.63; p<0.001), respectively. Overall, RDW exhibited a sizeable diagnostic performance for predicting 1-month PTA-related complications after hospital discharge, displaying an area under the curve (AUC) of 0.68 (95% CI, 0.55–0.81; p=0.004) (*Figure 1*). An even better efficiency could be observed for predicting early reocclusion after hospital discharge, wherein the AUC of delta RDW was 0.74 (95% CI, 0.57–0.91; p=0.002). A delta RDW of 1.025 was associated with 0.86 sensitivity and 0.72 specificity for predicting 1-month reocclusion after hospital discharge.

Discussion

The RDW is a simple, rapid and inexpensive parameter, reflecting the average heterogeneity of erythrocytes volumes (i.e., anysocytosis), which can now be generated by the vast majority of hematological analyzers along with other data of the complete blood cell count (CBC) (9). Several lines of evidence now attest that enhanced anysocytosis is commonplace in patients with a large number of human pathologies, including cardiovascular disorders (10), and that increased RDW values also reliably predict morbidity, hospital readmission and death (11, 12). Although several previous studies showed that anysocytosis may be associated with adverse outcome in patients undergoing CABG, percutaneous coronary angioplasty (PCA), percutaneous coronary intervention (PCI) and even postinterventional thrombolysis for acute coronary syndrome (7, 13–18), no information has been published to best of our knowledge on its diagnostic efficiency for predicting complications or adverse outcomes in patients undergoing PTA for severe forms of PAOD.

Some interesting conclusions can hence be made from the results obtained in this observational retrospective study. We first observed that PAOD patients had higher RDW and lower hemoglobin values than ostensibly healthy controls. These two parameters may hence be of value for non-invasive assessment of patients with suspected PAOD, or even for identifying a subset of patients at higher risk of developing PAOD. Even more importantly, we observed for the very first time that the in-hospital variation of RDW (i.e., the ratio between RDW values measured at hospital admission and discharge) was a significant predictor of early adverse outcomes, wherein patients with a delta RDW >1 had 60% and 88% enhanced risk of developing 1-month PTA-related complications and early restenosis after hospital discharge, respectively. This finding is in accordance with previous evidence garnered from other cardiovascular disorders, and showing that in-hospital variation of RDW may be a useful predictor of mortality in patients with heart failure (19, 20), higher readmission or unexpected death in the intensive care unit (ICU) (21), but also significantly predicted early adverse events after CABG (7). This would lead us to conclude that routine calculation of delta RDW between values measured at hospital admission and discharge may be a valuable approach in all patients undergoing PTA, wherein those exhibiting an increase during hospital stay should then be more strictly monitored during follow-up, or even subjected to more aggressive pharmacological or behavioral management (e.g., enhanced burdens of physical exercise). On the other hand, it is not surprising that the RDW value at hospital admission was not associated with PTA complications after patient discharge (*Table II*), since hospital stay and surgical management may have both considerably contributed to profoundly modify erythrocyte biology, as previously seen in other studies (9). Albeit the lifespan of red blood cells into the circulation is comprised between 90–120 days under physiological conditions, some biological and metabolic triggers can promote sudden changes of erythrocyte volume, so that RDW variations may occasionally develop in few hours (22).

Regarding the putative biological mechanisms linking anysocytosis and PTA-related complications, especially reocclusion, the current view of restenosis pathophysiology entails a various and multifaceted number of molecular and cellular events, which are strongly influenced by a perturbation of erythrocyte biology. In particular, it has been convincingly demonstrated that an increased RDW value is significantly associated with endothelial damage and failure of vascular repair (23), with increased concentration of proinflammatory biomarkers (24), oxidative stress (25), decreased erythrocyte deformability and hence with impaired blood flow (26), as well as with a higher predisposition for developing thrombosis (27, 28). Irrespective of the fact that RDW may be a player or a simple bystander in many of these biological pathways (29), all these factors are also important triggers, or precipitating factors, of restenosis after percutaneous angioplasty (5).

The CBC provides very useful clinical information and it might sometimes happen that physicians will not be using all the potential of this important test, including clinical use of RDW data. Although larger prospective investigations are needed to confirm our preliminarily findings, the results of this study, showing that in-hospital variation of RDW may be a noninvasive and reliable predictor of complications early after hospital discharge in patients who underwent PTA, suggest that this parameter may play a role for management and for guiding the clinical decision making of PTA patients immediately after hospital discharge.

Conflict of interest statement

The authors stated that they have no conflicts of interest regarding the publication of this article.

References

1. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. BMJ 2018; 360: j5842.
2. Veraldi GF, Mezzetto L, Macrì M, Criscenti P, Corvasce A, Poli R Comparison of endovascular versus bypass surgery in femoropopliteal TASC II D lesions: a single-centre study. Ann Vasc Surg 2018; 47: 179–87.
3. Aboyans V, Ricco JB, Bartelink MEL, Björck M, Brodmann M, Cohnert T, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the European Stroke Organization (ESO). The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J 2018; 39: 763–816.
4. Schillinger M, Minar E. Restenosis after percutaneous angioplasty: the role of vascular inflammation. Vasc Health Risk Manag 2005; 1: 73–8.
5. Geary RL, Clowes AW. Epidemiology and Pathogenesis of Restenosis. In: Duckers HD, Nabel EG, Serruys PW, editors. Essentials of Restenosis. Humana Press; New Jersey; 2007.
6. Tsakiris DA, Tschöpl M, Jäger K, Haefeli WE, Wolf F, Marbet GA. Circulating cell adhesion molecules and endothelial markers before and after transluminal angioplasty in peripheral arterial occlusive disease. Atherosclerosis 1999; 142: 193–200.
7. Lee SI, Lee SY, Choi CH, Park CH, Park KY, Son KH. Relation between changes in red blood cell distribution width after coronary artery bypass grafting and early postoperative morbidity. J Thorac Dis 2018; 10: 4244–54.
8. Tosaka A, Soga Y, Iida O, Ishihara T, Hirano K, Suzuki K, et al. Classification and clinical impact of restenosis after femoropopliteal stenting. J Am Coll Cardiol 2012; 59: 16–23.
9. 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: 86–105.
10. Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular diseases. J Thorac Dis 2015; 7: E402–11.
11. Turcato G, Cervellin G, Luca Salvagno G, Zaccaria E, Bartucci G, David M, et al. The Role of Red Blood Cell Distribution Width for Predicting 1-year Mortality in Patients Admitted to the Emergency Department with Severe Dyspnoea. J Med Biochem 2017; 36: 32–8.
12. Abrahan LL 4th, Ramos JDA, Cunanan EL, Tiongson MDA, Punzalan FER. Red Cell Distribution Width and Mortality in Patients with Acute Coronary Syndrome: A Meta-Analysis on Prognosis. Cardiol Res 2018; 9: 144–52.
13. Ünlü B, Küme T, Emek M, Örmen M, Doğan Y, Şişman RA, Ergör G, Çoker C. Effect of blood cell subtypes lysis on routine biochemical tests. J Med Biochem 2018; 37: 67–77.
14. Uyarel H, Ergelen M, Cicek G, Kaya MG, Ayhan E, Turkkan C, 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: 138–44.
15. Karabulut A, Uyarel H, Uzunlar B, Çakmak M. Elevated red cell distribution width level predicts worse post-interventional thrombolysis in myocardial infarction flow reflecting abnormal reperfusion in acute myocardial infarction treated with a primary coronary intervention. Coron Artery Dis 2012; 23: 68–72.
16. Demirsoy HI, Ertural YD, Balci Ş, Çınkır Ü, Sezer K, Tamer L, Aras N. Profiles of circulating miRNAs following metformin treatment in patients with type 2 diabetes. J Med Biochem 2018; 37: 499–506.
17. Duman E, Kulaksızoglu S, Çifçi E, Ozulku M. Is there a real correlation between red cell distribution width and peripheral arterial disease? J Med Biochem 2017; 36: 309–13.
18. Akboga MK, Yayla C, Yilmaz S, Sen F, Balci KG, Ozcan F, et al. Increased red cell distribution width predicts occlusion of the infarct-related artery in STEMI. Scand Cardiovasc J 2016; 50: 114–8.
19. Ferreira JP, Girerd N, Arrigo M, Medeiros PB, Ricardo MB, Almeida T, et al. Enlarging Red Blood Cell Distribution Width During Hospitalization Identifies a Very High-Risk Subset of Acutely Decompensated Heart Failure Patients and Adds Valuable Prognostic Information on Top of Hemoconcentration. Medicine (Baltimore) 2016; 95: e3307.
20. Turcato G, Zorzi E, Prati D, Ricci G, Bonora A, Zannoni M, et al. Early in-hospital variation of red blood cell distribution width predicts mortality in patients with acute heart failure. Int J Cardiol 2017; 243: 306–10.
21. Tonietto TA, Boniatti MM, Lisboa TC, Viana MV, Dos Santos MC, Lincho CS, et al. Elevated red blood cell distribution width at ICU discharge is associated with readmission to the intensive care unit. Clin Biochem 2018; 55: 15–20.
22. Lippi G, Salvagno GL, Danese E, Tarperi C, Guidi GC, Schena F. Variation of red blood cell distribution width and mean platelet volume after moderate endurance exercise. Adv Hematol 2014; 2014: 192173.
23. Rodríguez-Carrio J, Alperi-López M, López P, Alonso-Castro S, Carro-Esteban SR, Ballina-García FJ, et al. Red cell distribution width is associated with endothelial progenitor cell depletion and vascular-related mediators in rheumatoid arthritis. Atherosclerosis 2015; 240: 131–6.
24. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med 2009; 133: 628–32.

25. Semba RD, Patel KV, Ferrucci L, Sun K, Roy CN, Guralnik JM, et al. Serum antioxidants and inflammation predict red cell distribution width in older women: the Women's Health and Aging Study I. Clin Nutr 2010; 29: 600–4.

26. 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: 211–6.

27. Wang P, Wang Y, Li H, Wu Y, Chen H. Relationship between the red blood cell distribution width and risk of acute myocardial infarction. J Atheroscler Thromb 2015; 22: 21–6.

28. Lippi G, Buonocore R, Cervellin G. Value of Red Blood Cell Distribution Width on Emergency Department Admission in Patients With Venous Thrombosis. Am J Cardiol 2016; 117: 670–5.

29. Lippi G, Cervellin G, Sanchis-Gomar F. Red blood cell distribution width and cardiovascular disorders. Does it really matter which comes first, the chicken or the egg? Int J Cardiol 2016; 206: 129–30.

Received: September 8, 2018

Accepted: December 5, 2018