Thrombosis Research 164 (2018) 4–8

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Red cell distribution width as a predictor of 1-year survival in ischemic stroke patients treated with intravenous thrombolysis

João Pinho[a,*], Sofia Alexandra Marques[b], Eduardo Freitas[c], José Araújo[a], Mariana Taveira[d], José Nuno Alves[a], Carla Ferreira[a]

[a] Neurology Department, Hospital de Braga, Sete Fontes, São Victor, 4715-243 Braga, Portugal
[b] School of Medicine, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal.
[c] Neurology Department, Hospital de Santa Luzia, Unidade Local de Saúde do Alto Minho, Estrada de Santa Luzia, 4904-858 Viana do Castelo, Portugal
[d] Internal Medicine Department, Hospital Pedro Hispano, Unidade Local de Saúde de Matosinhos, Rua Dr. Eduardo Torres, 4464-513 Senhora da Hora, Portugal.

ARTICLE INFO

Keywords:
Red cell distribution width
Ischemic stroke
Thrombolysis
Survival

ABSTRACT

Introduction: Red cell distribution width (RDW) has been found to be a prognostic marker in vascular diseases. Increased RDW predicted mortality and outcome after ischemic stroke however, the underlying mechanisms are unclear. Our study aimed to clarify the relation of RDW with stroke severity and 1-year survival.

Material and methods: Single-centre retrospective cohort study based on a prospective database of consecutive patients with acute anterior circulation ischemic stroke treated with intravenous thrombolysis (IVT) in a 9-year period. Clinical characteristics were collected from the registry. Additional information, namely pre-IVT RDW, was retrieved from individual patient records. Information concerning survival during the first year after stroke was collected from the national Health Data Platform.

Results: 602 patients were included. Patients in the higher RDW quartiles were older, and more frequently presented hypertension and cardioembolic etiology. RDW was higher in patients who presented early infection and a positive correlation was found between RDW and C-reactive protein. RDW was not associated with admission severity of stroke, neurological status 24 h after stroke or occurrence of symptomatic intracranial hemorrhage (sICH). Patients in the higher quartiles of RDW presented a lower 1-year survival ($p < 0.001$). After stepwise adjustment for variables of interest, including severity of ischemic stroke, sICH, and response to IVT, RDW remained a predictor of 1-year survival, specifically in patients ≥75 years and in patients with early post-stroke infection.

Conclusions: RDW is a predictor of 1-year survival in patients with ischemic stroke treated with IVT, specifically in older patients and those who develop early infection, and its prediction value is independent from stroke severity and response to IVT.

1. Introduction

Prognostic biomarkers in patients with acute ischemic stroke are an active area of research that showed the association of many venous blood markers with outcome. Whiteley and collaborators categorized these biomarkers in classes according to their role in the ischemic process, of which the most important are related to inflammation and hemostasis [1]. Red cell distribution width (RDW) is known to be associated with outcome in patients with cardiovascular disease such as coronary artery disease and heart failure [3], and also with the incidence of first acute coronary events [4] and all-cause mortality [5] in population-based studies. Several studies have also addressed the role of RDW in patients with cerebrovascular disease, but few studies included patients who had been treated with intravenous thrombolysis (IVT). A large prospective population-based study found no association of RDW at baseline and the incidence of stroke during a median follow-up period of 16 years [5]. However, another large prospective study of patients with coronary disease found that patients with higher RDW values at baseline more frequently presented stroke during a median follow up of 5 years [6]. Higher RDW values were also found in patients with previous stroke, when compared to individuals with no previous stroke [7]. Additionally, among patients with ischemic stroke, higher RDW was found to be predictive of mortality [7,8] and of poor 3-month functional outcome [8,9]. RDW is an erythrocyte index which represents the coefficient of variation of circulating red blood cell volume distribution, and its use in clinical practice is usually restricted to

* Corresponding author.
E-mail addresses: joao.pinho@hospitaldebraga.pt (J. Pinho), a69031@alunos.uminho.pt (S.A. Marques).

https://doi.org/10.1016/j.thromres.2018.02.002
Received 4 October 2017; Received in revised form 28 January 2018; Accepted 6 February 2018
Available online 07 February 2018
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Table 1
Characterization of the study population according to red cell distribution width quartiles (Q1–Q4).

	RDW-Q1 (n = 173)	RDW-Q2 (n = 156)	RDW-Q3 (n = 134)	RDW-Q4 (n = 139)	P
Age (years)	72 (60.5–78)	73 (64–79)	75.5 (68–81)	77 (70–82)	< 0.001
Female sex	96 (55.5)	87 (55.8)	84 (62.7)	78 (56.1)	0.562
Arterial hypertension	104 (60.1)	105 (66.7)	101 (75.4)	102 (73.4)	0.016
Diabetes	28 (16.2)	29 (18.6)	35 (26.1)	33 (23.7)	0.125
Dyslipidemia	75 (43.4)	69 (44.2)	65 (48.5)	55 (39.6)	0.524
Coronary heart disease	9 (5.2)	14 (9.0)	12 (9.0)	12 (8.6)	0.512
Previous antiplatelet therapy	44 (25.4)	39 (25.0)	47 (35.1)	50 (36.0)	0.055
Pevious anticoagulation	3 (1.7)	1 (0.6)	12 (9.0)	9 (6.5)	0.001
Admission NIHSS	14 (10–18)	14 (9–19)	14 (9–19)	16 (11 − 20)	0.215
Admission systolic blood pressure (mmHg)	143 (128–162)	147 (129–163)	148 (136–163)	148 (129–125)	0.352
Admission dyastolic blood pressure (mmHg)	81 (69–91)	81 (72–91)	82 (72–93.5)	80 (72–90)	0.619
Admission blood glucose (mg/dL)	124 (111–154)	127 (110–157)	121 (106–147)	132 (108.5–171)	0.094
ASPECTS 8–10	129 (74.6)	114 (75.3)	108 (81.2)	102 (73.4)	0.380
Hemoglobin (g/dL)	13.6 (12.8–14.8)	13.8 (12.8–14.8)	13.3 (12.5–14.6)	13.2 (12.0–14.2)	0.001
Mean corpuscular volume (fl)	91.8 (89.0–96.0)	91.0 (87.9–94.9)	90.6 (87.9–94.0)	90.4 (86.1–94.0)	0.009
Platelet count ($\times 10^3$)	215 (172–250)	197 (167–234)	199 (167–237)	208 (163–242)	0.172
Admission C-reactive protein (mg/dL)	3.1 (2.9–7.3)	2.9 (2.9–7.7)	3.4 (2.9–8.4)	5.5 (2.9–12.2)	0.009
Admission neutrophil-to-lymphocyte ratio	2.6 (1.9–4.4)	2.9 (1.9–3.0)	2.5 (1.8–3.9)	3.0 (2.1–4.8)	0.089
Symptom - needle time (min)	145 (111.5–185)	150 (110.5–194)	150 (110–195)	154.5 (119.5–200)	0.546
Hyperacute endovascular revascularization therapy	15 (8.7)	12 (7.7)	10 (7.5)	7(5.0)	0.666
NIHSS 24 h after IVT	9.5 (3–17)	9 (4–16)	3 (9–17)	12 (5.18)	0.201
Admission NIHSS – NIHSS 24 h after IVT (NIHSS improvement)	4 (0–8)	3 (0–7)	4 (0–8)	3 (0–7)	0.637
Symptomatic intracranial hemorrhage	9 (5.2)	4 (2.6)	6 (4.5)	11 (7.9)	0.209
Early post-stroke infection	32 (18.5)	24 (15.4)	37 (27.6)	44 (31.7)	0.002
Cardioembolism	68 (49.3)	67 (53.2)	65 (61.3)	83 (71.6)	0.002
Favorable outcome at 3 months[a]	76 (47.2)	66 (45.8)	65 (52.8)	44 (33.8)	0.019
1-Year mortality[b]	23 (13.5)	20 (13.0)	26 (20.2)	48 (35.0)	< 0.001

[a] Unavailable 3-month modified Rankin Scale in 44 patients.
[b] Unavailable mortality information in 11 patients.

characterization of anemia. It is still poorly understood whether RDW is just a risk marker for ischemic stroke, or if it is a causal risk factor directly involved in the pathogenic thrombotic mechanisms.

Our goal was to characterize RDW in a population of patient with acute ischemic stroke treated with IVT, to study its relation with stroke severity and early complications, and to analyze its impact in 1-year survival.

2. Material and methods

We conducted a retrospective cohort study based on the local registry of all adult patients admitted in a tertiary university hospital with the diagnosis of acute ischemic stroke, who were treated with IVT between February 2007 and July 2016. Patients with ischemic stroke in the vertebrobasilar territory and patients with no available pre-IVT complete blood count results were excluded. Our IVT protocol follows the European Stroke Organization recommendations, and major changes to the protocol occurred when the therapeutic window for thrombolysis was extended up to 4.5 h after symptom onset (October 2008) and when age > 80 years was no longer considered as an exclusion criteria for thrombolysis (June 2012). RDW was measured in all patients in venous blood samples collected immediately before starting IVT, which is part of the routine care of these patients. Fully automated RDW measurements were performed as a part of the routine laboratory tests in this condition, using Sysmex XE-5000 (Sysmex Inc., Kobe, Japan). Baseline clinical characteristics and imaging findings using admission Alberta Stroke Program Early CT Score (ASPECTS) [10] were collected from the registry. Pre-IVT laboratory results, National Institutes of Health Stroke Scale (NIHSS) 24 h after IVT, occurrence of early post-stroke infection, occurrence of symptomatic intracranial hemorrhage (sICH) and functional outcome at 3 months were collected by reviewing individual clinical records. Early post-stroke infection was defined as infection diagnosed by the treating physician in the first 48 h after admission, treatment with antibiotics started by the treating physician in the first 48 h after admission for presumed infection, or aural temperature ≥ 38.0 °C accompanied by clinical manifestations of infection in the first 48 h after admission. Isolated fever, isolated increased inflammatory markers and use of antibiotics without clinical manifestations of infection were not considered as evidence of infection. sICH was defined according to ECASS II [11]. Functional outcome was defined using the modified Rankin Scale (mRS), and mRS 0-2 was considered a favorable outcome. Information of death during the first year after ischemic stroke was collected from the Portuguese electronic Health Data Platform, which allows access to individualized information generated by the Portuguese Death Certificate Information System.

The study population was categorized in four groups according to the distribution of RDW in quartiles (Q1–Q4). The groups were compared using Pearson chi-square and Kruskal-Wallis tests as adequate. Spearman's correlation was used to analyze relation between continuous variables. Kaplan-Meier survival curves using death during the first year after ischemic stroke as endpoint were constructed, and differences between Q1–Q4 were tested with the log-rank test. Survival analysis with Cox regression models using death during the first year after stroke as endpoint were constructed using variables of interest as independent variables, which were selected based on known impact on outcome and mortality after ischemic stroke, and potential bias in the evaluation of the predictive role of RDW. The proportionality of hazards in Cox regression was confirmed in every model using Schoenfeld residuals analysis. Effect modification in the regression models, namely involving the RDW variable, was tested by including in the model 2-way interaction terms as independent variables. If a significant interaction was found and persisted after centering the continuous variables,

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