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Neutrophil-to-lymphocyte ratio improves outcome prediction of acute intracerebral hemorrhage

Simona Lattanzi*, Claudia Cagnetti, Claudia Rinaldi, Stefania Angelocola, Leandro Provinciali, Mauro Silvestrini

Neurological Clinic, Department of Experimental and Clinical Medicine, Marche Polytechnic University, Via Conca 71, Ancona 60020, Italy

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ABSTRACT

Background: The inflammatory response plays a role in determining the course of intra-cerebral hemorrhage (ICH) and immune parameters may have prognostic value. The aim of the study was to determine whether the peripheral leukocyte counts and neutrophil-to-lymphocyte ratio (NLR) were associated to 30-day functional status after ICH, and improved the accuracy of outcome prediction when added to the Modified ICH score.

Methods: We retrospectively identified consecutive patients with spontaneous ICH who underwent blood sampling and cranial CT neuroimaging within 24 h from onset. Total white blood cells (WBC), absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were collected, and the NLR computed as the ANC to ALC ratio. The study endpoint was 30-day functional status; poor outcome was defined as death or major disability (modified Rankin Scale score ≥ 3).

Results: Two hundred and eight patients were enrolled, of which 111 (53.4%) had a modified Rankin Scale score ≥ 3 at 30 days from ICH. At multivariate analysis, the WBC (adjusted odd ratio [$_{adj}$OR] for 1000 leukocytes increase 1.20, 95% confidence interval [CI] 1.05–1.38), ANC ($_{adj}$OR for 1000 neutrophils increase 1.34, 95% CI 1.14–1.57), ALC ($_{adj}$OR for 1000 lymphocytes increase 0.34, 95% CI 0.20–0.59) and NLR ($_{adj}$OR for 1-point increase 1.49, 95% CI 1.24–1.79) were independently associated with 30-day poor outcome. Predictive accuracy of the Modified ICH score was enhanced by adding the NLR.

Conclusions: The NLR was associated with 30-day mortality and morbidity after ICH, and improved the accuracy of outcome prediction when added to the Modified ICH score.

1. Introduction

Spontaneous intracerebral hemorrhage (ICH) accounts for 10% to 30% of all strokes and is characterized by high rates of mortality and residual disability among survivors [1]. Currently, no medical or surgical treatment has definitively proven to be effective, and the identification of reliable factors to allow early prognostication and risk stratification of patients still represents a clinical priority [2]. Although several grading scales have been proposed, they mostly account for the primary injury and early mass effect, including the hematoma volume, location, or intra-ventricular extension [3]. Conversely, the benefit to include markers synthesizing the pathophysiological processes which are triggered by cerebral hemorrhage and take part to secondary-induced damage, has been only marginally examined [4]. On this ground, there is compelling evidence that inflammatory response plays a role in determining the ICH course, and immune parameters may have prognostic value [5]. Remarkably, the neutrophil-to-lymphocyte ratio (NLR) is an easily available inflammatory index, which has been related to in-hospital mortality, early neurological deterioration and 3-month outcome in ICH patients [6–9]. However, the actual benefit of the NLR in the estimate of the ICH outcome in comparison to the traditional predictive models has not been fully investigated. The aim of this study was to explore the relationship between the peripheral leukocyte counts and NLR at admission with 30-day mortality and morbidity after ICH, and evaluate whether the addition of these variables to the Modified ICH score could improve the accuracy of outcome prediction.

2. Methods

2.1. Participants and study outcome

We retrospectively identified consecutive patients hospitalized at the Stroke Unit of the Marche Polytechnic University, Ancona, Italy from January 2008 to March 2017 for stroke syndrome due to acute

* Corresponding author.
E-mail address: alfierelattanzisimona@gmail.com (S. Lattanzi).

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spontaneous ICH who underwent admission routine blood sampling and cranial CT neuroimaging within 24 h from symptom onset. Demographics, medical history, National Institutes of Health Stroke Scale (NIHSS) [10] scores and blood pressure (BP) at admission were retrieved. The Modified ICH score was computed, as previously described [11]. Total white blood cells (WBC), absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were collected from admission blood work; the NLR was derived as the ratio of the ANC to ALC values. Baseline volume, topography (lobar, deep, brainstem, cerebellum), intraventricular hemorrhage (IVH) (presence versus absence) of ICHs were determined [12]. All CT scans were read by a single evaluator blinded to clinical and biochemical data. The previously validated ABC/2 or ABC/3 methods were used to estimate the hematoma volume for round and ellipsoid or irregularly and separately shaped haemorrhages, respectively [13]. These methods correlated well with more sophisticated planimetric volume measurements [14]. All patients received standard management according to current national guidelines for stroke [15]; CT angiography or conventional cerebral angiography were performed to assess the presence of any structural parenchymal or vascular abnormality. The study endpoint was the 30-day functional status assessed through the modified Rankin Scale (mRS) [16]; the occurrence of death or major disability (mRS ≥ 3) defined the poor outcome.

Patients presenting with secondary ICH or isolated intra-ventricular hemorrhage and patients receiving immunomodulatory or immunosuppressive treatment (e.g. corticosteroids, azathioprine, methotrexate, other cytostatic and biologicals agents as monoclonal antibodies) before admission were not included in the study.

2.2. Statistical analysis

Values are presented as mean ± SD or median (interquartile range [IQR]) for continuous variables and as the number (percent) of subjects for categorical variables. Comparisons were made through the Student *t*-test, Mann-Whitney test or Chi-squared test as appropriate. Linear regression analysis was performed to evaluate the association of WBC, ANC, ALC and NLR with baseline ICH volume and age. The associations between the WBC, ANC, ALC and NLR and the study endpoint were determined using logistic regression; the variables with p values < 0.05 from comparison of baseline characteristics and selected variables (age, initial NIHSS score, baseline volume and location of cerebral hematoma, IVH) were forced into multivariate analysis [7,8]. In order to evaluate the role of adding the WBC, ANC, ALC and NLR to the Modified ICH score, multivariate models with the Modified ICH score covariables (age, initial NIHSS, ICH volume, infratentorial origin, IVH) alone and with the Modified ICH score covariables plus each laboratory measure were generated. Overall fit of the models was assessed by the likelihood ratio (LR) χ^2 (1-degree-of freedom) test and McFadden adjusted R^2; discriminatory ability was evaluated by the receiver operating characteristic (ROC) analysis. Calibration was addressed by the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Hence, estimates of correct reclassifications were provided by the Integrated Discrimination Improvement (IDI) and Net Reclassification Improvement (NRI). IDI represents the change in discrimination slope, i.e. the difference between the mean estimated risk for cases and non-cases, of unconstrained compared to constrained model. In NRI analysis, the category risks defined by 10% and 90% thresholds were considered; thresholds were selected since the importance of the certainty of prognosis, as previously [4]. NRI quantifies the proportion of subjects correctly moved across the risk categories. Event-NRI was computed as the net upward reclassification for subjects experiencing the event; non-event NRI was the net downward reclassification for subjects without the event. Higher values of LR, McFadden adjusted R^2, IDI and NRI, and lower values of AIC and BIC imply better performance [17]. Results were considered significant for p values < 0.05 (two sided). Data analysis was performed using STATA/IC 13.1 statistical package (StataCorp LP, Texas, USA).

Table 1
Baseline characteristics according to 30-day outcome.

	Full cohort (n = 208)	Good outcome (n = 97)	Poor outcome (n = 111)	p value
Demographics				
Age (years)	66.7 (12.4)	66.7 (12.2)	66.6 (12.7)	0.969[a]
Female sex	76 (36.5)	36 (37.1)	40 (36.0)	0.872[b]
Caucasian	202 (97.1)	94 (96.9)	108 (97.3)	0.867[b]
Clinical history				
Hypertension	129 (65.5)	62 (63.9)	67 (60.4)	0.598[b]
Diabetes mellitus	44 (21.2)	24 (24.7)	20 (18.0)	0.236[b]
Hyperlipidemia	69 (33.2)	30 (30.9)	39 (35.1)	0.520[b]
Atrial fibrillation	20 (9.6)	11 (11.3)	9 (8.1)	0.430[b]
Coronary artery disease	24 (11.5)	14 (14.4)	10 (9.0)	0.222[b]
Prior stroke/TIA	15 (7.2)	7 (7.2)	8 (7.2)	0.998[b]
Current smoker	39 (20.1)	19 (21.4)	20 (19.1)	0.690[b]
Pre stroke medications				
Antiplatelet agents	42 (20.2)	21 (21.7)	21 (18.9)	0.625[b]
Oral anticoagulants	18 (8.7)	8 (8.3)	10 (9.0)	0.845[b]
Statins	61 (29.3)	32 (32.9)	29 (26.1)	0.278[b]
Antihypertensive drugs	107 (51.4)	54 (55.7)	53 (47.8)	0.254[b]
Admission				
Systolic BP (mm Hg)	150 (135–170)	145 (130–165)	140 (160–170)	0.026[c]
Diastolic BP (mm Hg)	80 (75–90)	80 (70–90)	80 (75–90)	0.362[c]
NIHSS score	9 (6–14)	7 (5–8)	12 (9–16)	< 0.001[c]
Brain imaging ICH parameters				
Volume (mL)	7.8 (3.3–15.1)	4.3 (2.3–9.8)	12.6 (6.4–21.0)	< 0.001[c]
Location				
Lobar	74 (35.6)	39 (40.2)	35 (31.5)	0.192[b]
Deep	123 (59.1)	50 (51.5)	73 (65.8)	0.037[b]
Brainstem	1 (0.5)	1 (1.0)	0 (0.0)	0.284[b]
Cerebellum	10 (4.8)	7 (7.2)	3 (2.7)	0.129[b]
Intraventricular hemorrhage	45 (21.6)	16 (16.5)	29 (26.1)	0.092[b]
Modified ICH score	1 (0–1)	0 (0–1)	1 (0–2)	< 0.001[c]
Time onset-to-sample	17.2 (15.4–18.8)	17.0 (14.9–18.8)	17.7 (15.6–18.9)	0.202[c]

Data are mean (SD) or median (IQR) for continuous, and n (%) for categorical variables. Abbreviations: BP = blood pressure; ICH = intracerebral hemorrhage; NIHSS = National Institute of Health Stroke Scale; TIA = transient ischemic attack.
[a] Two-sample *t*-test.
[b] Chi-squared test.
[c] Mann-Whitney test.

2.3. Standard protocol approvals

The study was approved by the local ethical committee and performed in accordance with the Declaration of Helsinki. The board allowed the study to be conducted without patients' consent because of the retrospective nature of the study.

3. Results

A total of 208 patients were recruited, of which 111 (53.4%) had a modified Rankin Scale score ≥ 3 at 30 days from ICH onset. Baseline characteristics according to patient subgroups are summarized in Table 1. Poor outcome patients had higher WBC (9.67 ± 4.01 versus 7.70 ± 2.22; p < 0.001), higher ANC (7.64 ± 3.86 versus 5.07 ± 1.94; p < 0.001), lower ALC (1.35 ± 0.68 versus 1.95 ± 0.65; p < 0.001), and higher NLR (7.16 ± 5.10 versus 2.95 ± 1.78; p < 0.001) (Table 2).

According to linear regression analysis, the laboratory parameters