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ORIGINAL ARTICLE

Systemic inflammation status at admission affects the outcome of intracerebral hemorrhage by increasing perihematomal edema but not the hematoma growth

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Abstract

Acute stress and inflammation responses are associated with worse outcomes in intracerebral hemorrhage (ICH) but the precise mechanisms involved are unclear. We evaluated the effect of neutrophil-to-lymphocyte ratio (NLR) in ICH outcome, with focus on hematoma expansion and early cerebral edema. In a retrospective study, we included all patients with primary ICH admitted to our center within 24-h from symptom onset from January 2014 to February 2015. We retrieved demographic and medical history data, Glasgow Coma Scale scores, blood cell counts, glucose, and C-reactive protein, and calculated NLR. We obtained hematoma volumes by computerized planimetry. Outcomes included independence at 90 days (modified Rankin scale 0–2), mortality at 30 days, significant hematoma expansion (> 33% or > 6 mL) and early cerebral edema causing significant midline shift (> 2.5 mm) at 24 h. We included 135 patients. NLR independently associated with independence at 90 days (adjusted odds ratio (aOR) 0.79, 95% CI 0.67–0.93, $p = 0.006$) significant cerebral edema (aOR 1.08, 95%CI 1.01–1.15, $p = 0.016$) but not hematoma expansion (aOR 0.99, 95%CI 0.94–1.04, $p = 0.736$). The severity of midline shift was positively correlated with NLR (adjusted beta = 0.08, 95% CI 0.05–0.11, $p < 0.001$). In ICH, an immediate and intense systemic inflammatory response reduces the likelihood of a better functional outcome at 90 days, which is more likely to be explained by perihematomal edema growth than due to a significant hematoma expansion. These findings could have implications in new treatment strategies and trial designs, which endpoints tend to target exclusively hematoma enlargement.

Keywords Intracerebral hemorrhage · Neutrophils · Inflammation · Hematoma · Brain edema

Introduction

The increasing trends in incidence and mortality of spontaneous intracerebral hemorrhage (ICH) constitute a major challenge [1], because studies done so far found no robust evidence for any specific treatment. Acute lowering of blood pressure reached no definitive results in two recent clinical trials in terms of functional outcome [2, 3] despite the fact that both proved to significantly reduce the rate of hematoma expansion. Therefore, other factors must be sought.

Acute stress and inflammation also have an important role in the pathophysiology of acute ICH [4]. Secondary brain injury results from the accumulation of intraparenchymal toxic blood components, which can be enhanced by the external inflammatory environment [4]. This leads to irreversible disruption of the components of the neurovascular unit and cell death through several pathways, namely, excitotoxicity, oxidative stress and inflammation [4]. Animal studies support the fact that high levels of metabolic stress lead to a reduction of perihematomal autophagy, a physiologic pathway activated in acute stress response to ICH [5, 6]. Recent attention has been given to neutrophil indexes as simple biomarkers of the intensity of systemic inflammation [7]. Particularly, the neutrophil-to-lymphocyte ratio (NLR) has been linked to increased mortality [8, 9], and functional outcome [7, 8] but the precise mechanisms for this effect are not clear. Other reactive inflammatory markers

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like platelet-to-lymphocyte ratio (PLR) have not been thoroughly accessed before [10].

We aimed to study the predictive value of admission NLR, as compared to neutrophilia, PLR, C-reactive, and glycemia, on significant hematoma growth and early cerebral edema at 24 h in patients with spontaneous ICH as well as mortality and functional outcome at 90 days.

Methods

Patient selection

We retrospectively analyzed all consecutive patients with primary ICH admitted to Centro Hospitalar Universitário São João (Porto, Portugal) between January 2014 and February 2015 that performed head computerized tomography (CT) within 24 h from symptom onset. Patients were excluded if they had: (1) evidence of traumatic intracranial bleeding; (2) neoplastic or vascular lesion presumed to be the underlying cause of the hemorrhage; (3) hemorrhagic transformation of a cerebral infarct; (4) massive hemorrhage judged by the clinicians to have a very poor prognosis leading to the withdrawal of usual intensive care management; (5) unavailable computerized tomography (CT). The study protocol was approved by the Ethics Committee of Centro Hospitalar Universitário São João.

Parameter acquisition

We assessed electronic medical records and retrieved demographic and clinical variables such as sex, age, vascular risk factors, chronic medication, admission Glasgow Coma Scale (GCS) score, National Institutes of Health Stroke Scale (NIHSS) score, systolic and diastolic arterial blood pressure. We also reviewed acute therapies to reverse anticoagulation and surgical interventions performed, intensive care unit charts, and occurrence of infection within the first 48 h. We registered laboratory results of admission absolute counts of total white blood cells, neutrophil, lymphocyte and platelets, C-reactive protein, glucose and of lipidogram. We calculated NLR (neutrophil/lymphocyte counts), neutrophilia (neutrophil/total white blood cells count × 100%), and platelet/lymphocyte count ratio (PLR). We calculated ICH and Functional Outcome in Patients with Primary Intracerebral Hemorrhage (FUNC) scores. The ICH Score is a simple and reliable scale that predicts mortality at 30 days in primary ICH, which includes initial GCS score, age and hematoma location and volume [11]. In turn, the FUNC score was validated to predict functional independence at 3 months and includes GCS score, age, previous cognitive impairment and hematoma location and volume [12]. These validated outcome scores were obtained to summarize relevant variables into a composite variable for adjustment in the multivariate analyses.

Image analysis

We retrieved the original DICOM data from the imaging database (SECTRA) of the admission CT and the follow-up CT scan performed within 24 to 36 h from ICH onset. The imagiological evaluation was carried out by an experienced neuroradiologist (FC) who was unaware of the other variables and outcomes. The area of the hematoma was calculated using the Osirix® software version 8.0 with manual slice-to-slice ROI tool, followed by manual correction. Significant hematoma growth was considered when an expansion of > 33% or > 6 mL was present between the two CT evaluations. Presence of intraventricular blood was registered but not included in the total hematoma volume. At 24-h CT, we registered the presence of cerebral edema causing midline shift (MLS) and quantified it in millimeters. Midline shift (MLS) was determined by creating a line connecting the anterior and posterior insertions of the falx cerebri, and measuring a perpendicular distance from the line to the septum pellucidum, at the level of the foramen of Monro.

Outcome measures

The imagiological outcomes included significant hematoma expansion (> 33% or > 6 mL) and early significant cerebral edema causing midline hematoma shift (> 2.5 mm) at 24 h. Clinical outcomes were mortality at 30 days and favorable functional independence (modified Rankin scale (mRS) score 0–2) at 90 days.

Statistical analysis

Normality of variables was determined by Shapiro–Wilk test. We compared the baseline categorical and continuous independent variables between groups of outcome with Chi-square test or Student's *T* test/Mann–Whitney test, respectively.

The predictive value of NLR, neutrophilia, PLR, C-reactive protein, glucose for significant hematoma expansion and cerebral edema causing MLS, death at 30 days, independence at 90 days, were characterized by odds ratios (OR) and respective 95% confidence interval (CI) obtained through logistic regression. We adjusted them to ICH score for death at 30 days and FUNC score for independence at 90 days in multivariate analysis. For significant hematoma expansion, we adjusted to a probability score validated in the pooled analysis of recent ICH trials, which can be obtained individually by the formula probability $= -4.426 - 0.230 \times \text{onset-to-CT time (h)} - 0.0776 \times \text{volume} + 1.196 \times \sqrt{\text{volume}} + 0.310 \times \text{antiplatelet} + 1.065 \times \text{anticoagulant}$, where

antiplatelet/anticoagulant is an indicator variable for previous medication taking values 1 for "yes" and 0 for "no" [13]. For cerebral edema, we adjust to initial hematoma volume, which was the only variable associated with this outcome in exploratory univariate logistic regression analysis, and to the presence of infection. NLR, PLR, glucose and CRP were non-normality distributed, and were log-transformed in multivariate analysis.

For further characterization, the whole range of clinical outcome of mRS at 3 months was compared among the NLR terciles with ordinal shift analysis modeling across all levels of the scale after we verified conformity to the assumption of a common proportional odds. We also used Spearman's correlations and linear regression to characterize the association between the hematoma expansion (absolute) and the degree in midline shift with log-transformed NLR. We used Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp, Armonk, NY). The significance level was fixed at $p < 0.05$.

Results

We identified 177 patients diagnosed with primary ICH and excluded 42 ($n = 16$ with secondary causes at follow-up studies; $n = 12$ with urgent surgery at admission; $n = 4$ massive hemorrhage with very poor prognosis; $n = 7$ missing admission CT; $n = 3$ patients without mRS), so that 135 remained in final analysis. Table 1 shows the characteristics of all cohort. Median (interquartile range) of age was 73 (64–80) years, baseline hematoma volume 10 (2.3–26) mL, admission NLR 4.3 (2.2–8.5), neutrophilia 74 (62–85) %, PLR 130 (88–242), glucose 141 (114–194) mg/dl, and C-reactive protein 6.7 (3.2–15.9).

Functional outcome and mortality

Independence at 90 days was achieved by $n = 29$ (22%) and mortality within 30 days in $n = 35$ (26%). In univariate analysis, independence at 90 days was significantly associated with higher lymphocytes count ($p = 0.008$), FUNC score ($p < 0.001$) and GCS score ($p < 0.001$), younger age ($p < 0.001$), lower values of NIHSS score ($p < 0.001$), ICH volume ($p = 0.021$), NLR ($p < 0.001$), neutrophilia ($p = 0.031$), PLR ($p = 0.001$), glucose ($p < 0.001$) and absence of infection within 48 h ($p = 0.035$) but not with C-reactive protein ($p = 0.113$) (Supplementary Table 1). Mortality at 30 days was significantly associated with higher values of ICH score ($p < 0.001$), NIHSS score ($p < 0.001$), ICH volume ($p < 0.001$), and blood glucose ($p < 0.001$), lower values of GCS score ($p < 0.001$),the presence of intraventricular hematoma ($p < 0.001$) and absence of infection within 48 h ($p = 0.049$) but not NLR ($p = 0.718$), neutrophilia

Table 1 Baseline characteristics of all patients

Variables	All cohort ($n = 135$)
Clinical and demographic	
Male sex	69 (66)
Age, years—median (IQR)	73 (64–80)
Arterial hypertension—*n* (%)	94 (70)
Smoking—*n* (%)	16 (12)
Dyslipidemia—*n* (%)	59 (44)
Diabetes mellitus—*n* (%)	41 (30)
Antiplatelet drugs—*n* (%)	37 (27)
Anticoagulation—*n* (%)	32 (24)
Statins—*n* (%)	48 (36)
NIHSS score—median (IQR)	10 (3–22)
Glasgow Coma Scale score—median (IQR)	14 (9–15)
Systolic ABP, mmHg—mean (SD)	160 (33)
Diastolic ABP, mmHg—mean (SD)	84 (20)
Laboratorial analysis	
Glucose, mg/dl—median (IQR)	141 (114–194)
LDL mg/dl—median (IQR)	106 (75–128)
HDL mg/dl—median (IQR)	44 (36–53)
Triglycerides mg/dl—median (IQR)	88 (73–115)
C-reactive protein, mg/l—median (IQR)	6.7 (3.2–15.9)
Leucocytes $\times 10^9$/l—median (IQR)	9.0 (7.2–11.8)
Neutrophils $\times 10^9$/l—median (IQR)	6.6 (4.4–9.8)
Lymphocytes $\times 10^9$/l—median (IQR)	1.5 (0.9 – 2.2)
Platelets $\times 10^9$/l—mean (SD)	207 (65.7)
Neutrophilia—mean (SD)	73 (14)
Neutrophil-to-lymphocyte ratio—median (IQR)	4.3 (2.2 – 8.5)
Platelet-to-lymphocyte ratio—median (IQR)	130 (88–242)
Hematoma characteristics and complications	
Time from symptom onset to 1st CT Scan in minutes—median (IQR)	194 (107.75–852)
Hematoma volume—median (IQR)	10 (2.3 – 26)
Hematoma expansion, mL—median (IQR)	18 (− 16.7 to + 99.1)
Location	
Lobar—*n* (%)	58 (43)
Deep—*n* (%)	50 (37)
Infratentorial—*n* (%)	27 (20)
Vitamin K—*n* (%)	23 (17)
Prothrombin complex—*n* (%)	21 (16)
External ventricular drainage—*n* (%)	8 (6)
Infection—*n* (%)	22 (16)
Urinary tract infection—*n* (%)	10 (45.5)
Pulmonary—*n* (%)	10 (45.5)
Others—*n* (%)	2 (9)
Prognostic scores	
FUNC score, median (IQR)	7 (5–8)
ICH score, median (IQR)	1 (1–2)

Values presented are medians (interquartile range), means (standard deviation) or counts (percentage)

NIHSS National Institutes of Health Stroke Scale, *FUNC* functional outcome in patients with primary intracerebral hemorrhage, *ICH* intracranial hemorrhage, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *ABP* arterial blood pressure

($p=0.085$), lymphocytes count ($p=0.944$), PLR ($p=0.845$), or C-reactive protein ($p=0.236$) (Supplementary Table 2). The presence of infection within 48 h was not significantly associated with inflammation markers including NLR, CRP, neutrophilia, lymphocytes count ($p=0.944$), PLR and glycemia in the acute phase ($p>0.05$) (Supplementary Table 3).

In multivariate logistic regression models (Table 2), NLR predicted independence at 90 days (adjusted OR (aOR) 0.80, 95% CI 0.67–0.94, $p=0.006$) but not mortality at 30 days (aOR 0.98, 95% CI 0.91–1.05, $p=0.561$). Glucose also predicted independence at 90 days (aOR 0.99, 95% CI 0.97–0.997, $p=0.015$) but not mortality at 30 days (aOR 1.01, 95% CI 0.998–1.02, $p=0.119$). PLR also predicted independence at 90 days (aOR 0.99, 95% CI 0.99–0.999, $p=0.020$) but not mortality at 30 days (aOR 0.998, 95% CI 0.993–1.002, $p=0.336$). CRP, neutrophilia and lymphocyte count were not significantly associated with functional outcome nor with mortality at 30 days ($p>0.05$).

The relationship of NLR and functional outcome was further characterized by comparing the distribution of every class of mRS scale among NLR terciles (Fig. 1). The highest NLR tercile showed a significant shift towards worse functional outcome categories which is more evident in mRS classes from 0 to 2 (T3 versus T1: ordinal shift analysis OR 2.77, 95% CI 1.29–5.94, $p=0.009$; T3 versus T2: 2.98, 1.37–6.49, $p=0.006$; T2 versus T1: 1.05, 0.51–2.19, $p=0.890$).

Imagiological outcomes

Significant hematoma expansion was documented in 63 (47%) patients and significant cerebral edema causing MLS in 50 (37%). In univariate analysis, significant hematoma expansion was related to previous anticoagulant use ($p=0.019$), but not NLR, neutrophilia, lymphocyte count, PLR, C-reactive protein, glucose or presence of infection within 48 h($p>0.05$) (Supplementary Table 4). Cerebral edema causing MLS was associated with lower levels of GCS score ($p<0.001$), higher values of NIHSS ($p<0.001$), hematoma volume ($p<0.001$), NLR ($p=0.023$), and neutrophilia ($p=0.006$), but not lymphocyte count, PLR, glucose, C-reactive protein or presence of infection within 48 h ($p>0.05$) (Supplementary Table 5). In multivariate logistic regression models (Table 3), NLR was not associated with hematoma expansion (aOR = 0.99, 95%CI 0.94–1.04, $p=0.737$) but predicted significant cerebral edema (aOR 1.08, 95%CI 1.02–1.15, $p=0.016$). PLR, neutrophilia, lymphocytes count, C-reactive protein and glucose were not associated with imagiological outcomes in adjusted analysis ($p>0.05$).

To further characterize the relationship between NLR with hematoma volume expansion and absolute value of midline shift at 24 h, we performed Spearman's correlations and represented them in scatter plots in Fig. 2. NLR was not correlated with absolute hematoma volume growth ($r=-0.330$, $p=0.117$). Instead, NLR positively correlated with the higher distance of midline shift ($r=0.256$, $p=0.005$) irrespective of baseline hematoma volume in linear regression analysis (adjusted beta = 0.927 (95% CI 0.06–1.80), $p=0.037$). This can be also inspected in Fig. 2, in which the positive relationship between NLR and midline shift is present in both subgroups with smaller (< 30 mL) and larger (≥ 30 mL) hematoma volumes.

Discussion

Our study confirms that a higher NLR at admission is associated with a reduced chance of a favorable functional outcome at 90 days, but it also clarifies that this effect is likely due to a higher risk of developing early significant edema and not driven by increased rates of hematoma expansion or early death. We were also able to show that NLR stands out from other acute stress and inflammatory biomarkers, namely PLR and glucose, which also independently predict functional outcome at 90 days; however, this effect was not due to hematoma expansion or development of early significant edema. Neutrophilia, lymphocytes count, and C-reactive protein showed no association with clinical or imagiological outcomes when adjusted to baseline severity.

The association of NLR with increased cerebral edema probably occurs because the NLR is a proxy for the local inflammatory response surrounding brain acute hematoma [7, 14]. In the brain, this response is particularly well documented in animal models and is characterized by infiltrating leukocytes, namely neutrophils and macrophages, and activated microglia, all contributing to the production of chemokines, cytokines, extracellular proteases and reactive oxygen species [14]. Interestingly, the inflammatory response after ICH occurs not only locally in the brain but it also involves the recruitment of peripheral leukocytes [15, 16]. These findings justify why peripheral neutrophil count can be credited to represent the active inflammation response soon after ICH and why it is linked to an increased perihematomal edema. Additionally, animal studies show that the build-up of secreted cytokines and chemokines by neutrophils occurs rapidly in hours [17] which explains why such an early assessment of NLR is already linked to increased cerebral secondary damage with impact in long-term functional recovery.

The role of acute inflammatory markers in ICH outcome has been studied before. One study found an association of NLR with ICH outcome but considered only mortality rates and not neurological disability [8]. Later on, Lattanzi et al. showed that there was a link between NLR and the risk of major disability (mRS 3–6) at 3 months but did not specify

Table 2 Prediction of functional outcome after spontaneous intracranial hemorrhage by logistic regression analysis

	Independence at 90 days (mRS 0 to 2)						Mortality at 30 days					
	Yes $n=29$	No $n=106$	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)*	p	Yes $n=35$	No $n=100$	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)**	p
NRL	2.3 (1.3–4.7)	4.8 (2.6–11)	0.77 (0.66–0.91)	0.002	0.80 (0.67–0.94)	0.006	4.4 (2.1–13)	4.2 (2.2–8.0)	1.03 (0.98–1.09	0.236	0.98 (0.91–1.05)	0.561
PLR	99 (59–148)	141 (94–258)	0.99 (0.99–0.998)	0.004	0.99 (0.99–0.999)	0.020	127 (90–255)	131 (85–229)	1.00 (0.998–1.00)	0.426	0.998 (0.993–1.002)	0.336
Neutrophilia, %	68 (51–77)	76 (63–86)	0.97 (0.94–0.995)	0.020	0.98 (0.95–1.01)	0.123	79 (65–87)	73 (61–84)	1.02 (0.995–1.05)	0.107	0.99 (0.94–1.03)	0.498
Lymphocytes $\times 10^9$/l	1.99 (1.26–2.70)	1.42 (0.84–2.10)	1.21 (1.01–1.45)	0.040	1.18 (0.97–1.48)	0.106	1.53 (0.80–2.72)	1.54 (0.94–2.17)	1.10 (0.93–1.30)	0.267	1.15 (0.89–1.48)	0.296
C-reactive protein, mg/dl	4.6 (2.0–12.0)	7.2 (3.5–16.0)	0.99 (0.97–1.01)	0.339	0.99 (0.98–1.01)	0.359	8.9 (3.2–26)	6.5 (3.0–12.5)	1.01 (0.997–1.02)	0.152	1.01 (1.00–1.02)	0.063
Glycemia, mg/dl	122 (103–127)	148 (117–200)	0.98 (0.97–0.99)	0.001	0.99 (0.97–0.997)	0.015	166 (142–219)	129 (109–179)	1.01 (1.01–1.02)	0.001	1.01 (0.998–1.02)	0.119

Values presented are medians (interquartile range)

mRS modified Rankin Scale, *NRL* neutrophil-to-lymphocyte ratio, *PLR* platelet to lymphocyte ratio

*Adjusted to presence of infection and FUNC score which includes age, Glasgow Coma Scale score, hematoma volume and location, and previous cognitive impairment;

**Adjusted to the presence of infection and ICH score which includes age, Glasgow Coma Scale score, hematoma volume, and intraventricular and infratentorial hematoma location

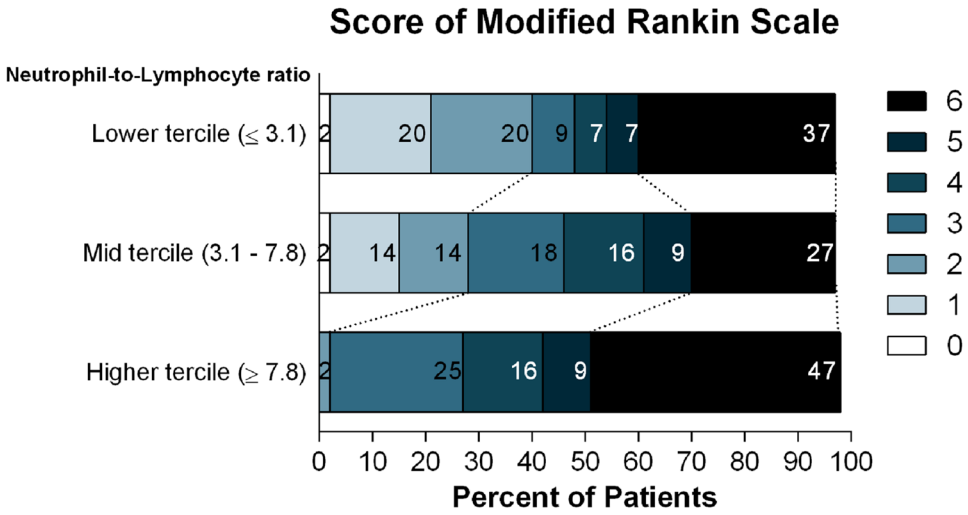

Fig. 1 Distribution of disability on modified Rankin Scale at 90 days (which ranges from 0 to 6, with higher scores indicating more severe disability) among terciles of neutrophil-to-lymphocyte ratio. Dotted lines depict the cut-offs used for binary outcomes of this study (independence and mortality). The numbers in the bars are percentages of patients who had each score. For the statistical analysis, consult "Results"

the underlying mechanism responsible for this association. Our results show that acute inflammation affects outcome mainly due to the development of significant perihematomal edema and not hematoma growth [7]. This is especially important since most recent trials in ICH focused on the intensive reduction of blood pressure, which seems to effectively prevent hematoma growth but did not reach conclusive results on functional outcome [2, 3]. This could be due to the fact that reduced blood pressure does not change perihematomal edema [18]. Nevertheless, AA Divani et al. demonstrated that systolic blood pressure variability (SBPV) may be associated with poor outcome in patients with ICH; however, no statistically significant association between SBPV and hematoma expansion was found, postulating that high SBPV may enhance perihematomal edema [19], a point to take into account in future trials.

In a recent study, an association between perihematomal edema and NLR with worse outcome was reported but they assessed cerebral edema and NLR at its peak around the end of first week [20], which did not answer the question whether inflammation levels are a reflection of worsening edema or causing it. In contrast, our study shows that admission NLR may already be a good marker of functional outcome and probably useful to tailor specific anti-inflammatory strategies in future trials. The use of more sophisticated semiautomatic algorithm could be useful in further investigations since it provides a more refined measurement of the perihematomal edema volume [21].

Despite the predictive value of NLR, our study did not demonstrate an association between functional independence, mortality or imagiological scores with lymphocyte count nor neutrophilia, both used to calculate NLR. Other studies have already showed that NLR outperformed leukocyte counts as predictors of neurological worsening [22]. Independently each inflammation marker seems to be insufficient to predict outcome; however, by combining them into NLR, the predictive value is greatly improved, confirming NLR as a more reliable predictor of functional outcome.

PLR and C-reactive protein are also markers of systemic inflammation. Differently from NLR, these markers have been correlated to chronic inflammation that occurs in atherosclerotic disease [23] and cancer [24] or in acute thrombotic diseases like pulmonary embolism [25]. In our study, PLR showed an association to clinical outcome represented by independence at 90 days although this effect was not due to significant midline shift or hematoma expansion. One could argue that mechanisms other that inflammation may be at effect here, or even pro and anti-inflammatory mechanisms at the same time producing no influence in the net result of edema. In fact, animal models of ICH showed that thrombin produced on the plasma membrane of platelets and leucocytes is released early in the setting of ICH, activating the inflammatory complement cascade. Although C3-deficient mice displayed improved behavioral outcomes after hemorrhage, C5-deficient mice showed only small increases in edema after ICH, suggesting that the various components of the complement cascade may play distinct roles after ICH [15].

Previous use of anti-platelet drugs could also interfere with platelet function and distort the value of PLR as marker of active inflammation. C-reactive protein, contrary to the acute cellular response measured by NLR, is a marker of slow humoral inflammatory response, meaning its prognostic value could be found later on the course of the ICH [26]. Also, concentrations of C-reactive protein and its predication values on a variety of stroke phenotypes are influenced by the ethnic genome background in different racial groups, sex, and the environment, limiting its use as prognostic marker in ICH [27]. This could explain the lack of prognostic information of C-reactive protein at presentation found in our study. Understanding

Table 3 Prediction of significant hematoma expansion or early significant cerebral edema after spontaneous intracranial hemorrhage by logistic regression analysis

	Significant hematoma expansion (> 6 mL or 33% at 24 h)						Significant early cerebral edema (midline shift > 2.5 mm at 24 h)					
	Yes $n = 63$	No $n = 72$	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)*	p	Yes $n = 50$	No $n = 85$	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)**	p
NRL	4.30 (2.27–8.11)	4.37 (2.12–8.93)	0.99 (0.94–1.04)	0.744	0.99 (0.94–1.04)	0.737	8.06 (1.68–13.1)	3.54 (2.2–6.07)	1.09 (1.03–1.16)	0.005	1.08 (1.02–1.15)	0.016
PLR	133 (90–244)	127 (83–241)	1.00 (0.997–1.01)	0.951	1.00 (0.997–1.003)	0.899	153 (84–271)	126 (89–195)	1.00 (1.00–1.01)	0.053	1.00 (1.00–1.01)	0.094
Neutrophilia, %	74 (62–85)	75 (61–85)	1.00 (0.98–1.02)	0.995	1.00 (0.98–1.02)	0.991	83 (68–88)	71 (62–80)	1.03 (1.00–1.06)	0.035	1.02 (0.99–1.05)	0.153
Lymphocytes $\times 10^9$/l	1.34 (0.89–2.09)	1.56 (0.95–2.38)	0.97 (0.83–1.15)	0.760	0.98 (0.83–1.16)	0.819	1.07 (0.80–2.54)	1.56 (1.14–2.15)	1.13 (0.95–1.34)	0.177	1.13 (0.94–1.35)	0.186
C-reactive protein, mg/dl	7.9 (3.6–16)	6.4 (2.7–12.8)	0.996 (0.99–1.01	0.464	1.00 (0.99–1.01)	0.535	8.3 (3.5–20.1)	6.4 (2.7–13)	1.00 (0.99–1.01)	0.536	1.00 (0.99–1.01)	0.499
Glycemia, mg/dl	141 (113–194)	140 (116–125)	0.998 (0.99–1.00)	0.457	1.00 (0.99–1.01)	0.569	155 (120–205)	132 (114–187)	1.01 (0.998–1.01)	0.160	1.00 (0.99–1.01)	0.869

Values presented are medians (interquartile range)

NRL neutrophil-to-lymphocyte ratio, *PLR* platelet to lymphocyte ratio

*Adjusted to the presence of infection and a computed probability score based on Salman et al. [13] which includes time of symptom onset to CT, hematoma volume, previous use of antiplatelet and anticoagulant

**Adjusted to the presence of infection and baseline hematoma volume

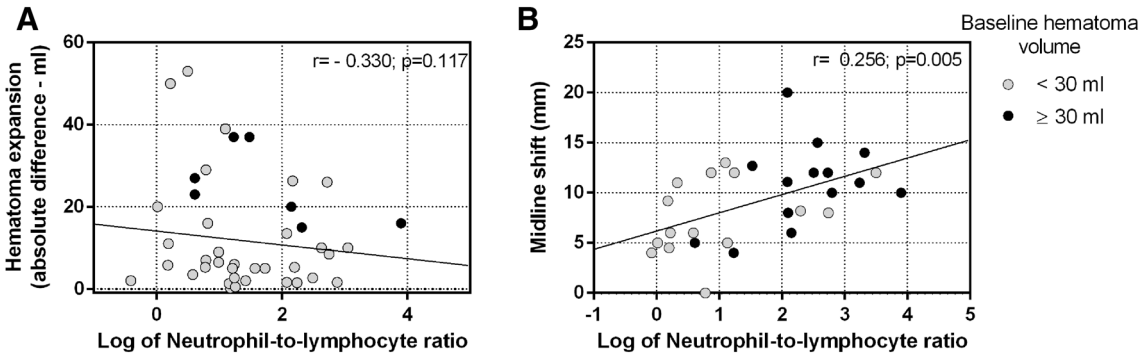

Fig. 2 Scatterplots showing the relationships between log-transform neutrophil-to-lymphocyte ratio and absolute volume expansion and absolute value of midline shift at 24 h. Subgroup admission hematoma volumes > 30 and ≤ 30 mL are represented by black and grey lines and dots

the different inflammatory pathways and respective biomarkers involved in ICH seems to be crucial to the development of novel drugs in future trials.

There was also an independent association between blood glucose levels and functional status at 90 days but neither with hematoma expansion or cerebral edema, contrary to animal models of ICH that showed that acute hyperglycemia and ICH with high-glucose blood hematoma not only exacerbated neurological function but also brain edema.[5]. In fact, previous studies also find a positive relationship of blood glucose and outcome on survival and long-term functional status.[28]. When we adjusted to baseline severity (ICH score), the association of glucose in multivariate analysis lost statistical significance meaning that initial hyperglycemia is correlated with ICH severity and not independently related to mortality. However, we should also consider the possibility of hyperglycemia at admission reflecting physiologic post-prandial increase rather than a systemic stress/inflammatory response which might blur the relations between this variable and outcomes measures. This is reinforced by SAMURAI–ICH study [29], in which glycemic levels were only related to outcome at 24 h after admission but not at presentation. This trial studied hematoma expansion and did not address the perihematomal edema as an outcome.

The presence of infection within 48 h of symptom onset correlated with worse functional status at 3 months; however, it also correlated with lower mortality at 30 days. These findings need to be considered on the acute phase of measurements. It is possible that patients with intracerebral hemorrhages associated with worse outcome factors and with higher probability of dying, had their signs and symptoms of infection masked by their neurological status. However the ones with better prognosis factors on admission, had their infections diagnosed and treated, explaining why in these patients the presence of infection could have had a worse impact on functional outcome but not on mortality.

Despite these associations, the presence of infection was not associated with variations on all inflammation markers and was taken into account on the multivariate analysis.

The NLR is an accessible and inexpensive marker that may be applied to ICH prognosis determination along with other known parameters [30]. Preclinical and clinical research suggests that ICH outcome is strongly influenced by a variety of factors related to metabolic homeostasis that may act either at the brain site of damage and systemic level influencing the neurovascular recovery and systemic complications, whose identification could aid to identify the variables that may serve to improve prognostic algorithms and identify future target of treatment in stroke patients [27, 31, 32].

Our study highlights the fact that NLR seems to be the best inflammation-related prognostic marker among simple and inexpensive indexes to be used in ICH and previous studies have highlighted the ability of NLR to improve outcome prediction only at 30 days when added to a modified ICH score model [33]. However, the systemic inflammatory pathways responsible for NLR variations and functional outcome prognosis after ICH needs to be explored. A recent review on Neutrophil-to-Lymphocyte Ratio in Acute Cerebral Hemorrhage by Lattanzi sheds some light on the different inflammatory pathways possibly implicated on ICH, which may involve neutrophil-induced neurotoxicity, with resulting in increase of capillary permeability, blood–brain barrier breakdown and cellular swelling, impacting negatively ICH functional recovery [34]. More specific pro-inflammatory molecules [7] could be of special interest to be further investigations in the future. This could reveal to be useful for selection or risk stratification of patients and possibly pharmacological interventions.

Limitations

Our study shares all the limitations of retrospective analysis. Also, we were not able to exclude patients with "do not resuscitate orders" which could influence the outcome.

However, this normally occurs in the presence of very severe ICH cases and would be reflected in FUNC and ICH scores that were used in multivariate analysis. Perihematomal edema usually develops more intensively after 1 week from ICH occurrence. In our study, we measured it at 24 h, and at this timing it might fail to detect the peak formation of perihematomal formation. Still, edema with midline shift was documented in a third of all cohort already at the early period of our study, which allows the study of NLR effects more precociously and at the same time frame as hematoma expansion. A more sophisticated method to measure perihematomal edema by software, without the use of midline shift as a surrogate, could have helped eliminate the bias of edema measurement depending on hematoma location. Additionally, another possible bias is the presence of hyperacute bleeding, which is hypodense on CT, that might be erroneously interpreted as early edema.

We were not able to include time from symptom onset to blood draw when analyzing the association between NLR and the outcomes measured, which could have somehow influenced the results.

Conclusions

In ICH, an immediate and intense systemic inflammatory response reduces the likelihood of a better functional outcome at 90 days, which is more likely to be explained by perihematomal edema growth than due to a significant hematoma expansion. These findings could have implications in new treatment strategies and trial designs with endpoints that tend to target exclusively hematoma enlargement.

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Compliance with ethical standards

Conflict of interest Sérgio Fonseca, Francisca Costa, Mafalda Seabra, Rafael Dias, Adriana Soares, Celeste Dias, Elsa Azevedo, and Pedro Castro declare that they have no conflict of interest to disclose.

Ethical approval This work adheres to ethical guidelines and the study has received ethical approval by the Ethics Committee of Centro Hospitalar Universitário São João.

References

1. Feigin VL, Krishnamurthi RV, Parmar P, Norrving B, Mensah GA, Bennett DA, Barker-Collo S, Moran AE, Sacco RL, Truelsen T (2015) Update on the global burden of ischemic and hemorrhagic stroke in 1990–2013: the GBD 2013 study. Neuroepidemiology 45(3):161–176
2. Qureshi AI, Palesch YY, Barsan WG, Hanley DF, Hsu CY, Martin RL, Moy CS, Silbergleit R, Steiner T, Suarez JI (2016) Intensive blood-pressure lowering in patients with acute cerebral hemorrhage. N Engl J Med 375(11):1033–1043
3. Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, Lindley R, Robinson T, Lavados P, Neal B, Hata J, Arima H, Parsons M, Li Y, Wang J, Heritier S, Li Q, Woodward M, Simes RJ, Davis SM, Chalmers J (2013) Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 368(25):2355–2365. https://doi.org/10.1056/NEJMoa1214609
4. Aronowski J, Zhao X (2011) Molecular pathophysiology of cerebral hemorrhage: secondary brain injury. Stroke 42(6):1781–1786
5. Liu R-Y, Wang J-J, Qiu X, Wu J-M (2014) Acute hyperglycemia together with hematoma of high-glucose blood exacerbates neurological injury in a rat model of intracerebral hemorrhage. Neurosci Bull 30(1):90–98
6. Chiu C-D, Chen C-CV, Shen C-C, Chin L-T, Ma H-I, Chuang H-Y, Cho D-Y, Chu C-H, Chang C (2013) Hyperglycemia exacerbates intracerebral hemorrhage via the downregulation of aquaporin-4: temporal assessment with magnetic resonance imaging. Stroke 44(6):1682–1689
7. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M (2016) Neutrophil-to-lymphocyte ratio predicts the outcome of acute intracerebral hemorrhage. Stroke 47(6):1654–1657
8. Giede-Jeppe A, Bobinger T, Gerner ST, Sembill JA, Sprügel MI, Beuscher VD, Lücking H, Hoelter P, Kuramatsu JB, Huttner HB (2017) Neutrophil-to-lymphocyte ratio is an independent predictor for in-hospital mortality in spontaneous intracerebral hemorrhage. Cerebrovasc Dis 44(1–2):26–34
9. Wang F, Hu S, Ding Y, Ju X, Wang L, Lu Q, Wu X (2016) Neutrophil-to-lymphocyte ratio and 30-day mortality in patients with acute intracerebral hemorrhage. J Stroke Cerebrovasc Dis 25(1):182–187
10. Zhang W, Shen Y (2018) Platelet-to-lymphocyte ratio as a new predictive index of neurological outcomes in patients with acute intracranial hemorrhage: a retrospective study. Med Sci Monit 24:4413–4420. https://doi.org/10.12659/MSM.910845
11. Tuhrim S (2001) The ICH score-A simple, reliable grading scale for intracerebral hemorrhage—Editorial Comment. Lippincott Williams & Wilkins, Philadelphia
12. Rost NS, Smith EE, Chang Y, Snider RW, Chanderraj R, Schwab K, FitzMaurice E, Wendell L, Goldstein JN, Greenberg SM (2008) Prediction of functional outcome in patients with primary intracerebral hemorrhage: the FUNC score. Stroke 39(8):2304–2309
13. Salman RA-S, Frantzias J, Lee RJ, Lyden PD, Battey TW, Ayres AM, Goldstein JN, Mayer SA, Steiner T, Wang X (2018) Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. Lancet Neurol 17(10):885–894
14. Gong C, Hoff JT, Keep RF (2000) Acute inflammatory reaction following experimental intracerebral hemorrhage in rat. Brain Res 871(1):57–65
15. Askenase MH, Sansing LH (2016) Stages of the inflammatory response in pathology and tissue repair after intracerebral hemorrhage. Semin Neurol 36(3):288–297. https://doi.org/10.1055/s-0036-1582132
16. Dickens AM, Tovar YRLB, Yoo SW, Trout AL, Bae M, Kanmogne M, Megra B, Williams DW, Witwer KW, Gacias M, Tabatadze N, Cole RN, Casaccia P, Berman JW, Anthony DC, Haughey NJ (2017) Astrocyte-shed extracellular vesicles regulate the peripheral leukocyte response to inflammatory brain lesions. Sci Signal 10(473):eaai7696. https://doi.org/10.1126/scisignal.aai7696
17. Mracsko E, Veltkamp R (2014) Neuroinflammation after intracerebral hemorrhage. Front Cell Neurosci 8:388. https://doi.org/10.3389/fncel.2014.00388

18. Anderson CS, Huang Y, Arima H, Heeley E, Skulina C, Parsons MW, Peng B, Li Q, Su S, Tao QL, Li YC, Jiang JD, Tai LW, Zhang JL, Xu E, Cheng Y, Morgenstern LB, Chalmers J, Wang JG, Investigators I (2010) Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). Stroke 41(2):307–312. https://doi.org/10.1161/STROKEAHA.109.561795
19. Divani AA, Liu X, Di Napoli M, Lattanzi S, Ziai W, James ML, Jafarli A, Jafari M, Saver JL, Hemphill JC, Vespa PM, Mayer SA, Petersen A (2019) Blood Pressure variability predicts poor in-hospital outcome in spontaneous intracerebral hemorrhage. Stroke 50(8):2023–2029. https://doi.org/10.1161/strokeaha.119.025514
20. Volbers B, Giede-Jeppe A, Gerner ST, Sembill JA, Kuramatsu JB, Lang S, Lucking H, Staykov D, Huttner HB (2018) Peak perihemorrhagic edema correlates with functional outcome in intracerebral hemorrhage. Neurology 90(12):e1005–e1012. https://doi.org/10.1212/wnl.0000000000005167
21. Gusdon AM, Gialdini G, Kone G, Baradaran H, Merkler AE, Mangat HS, Navi BB, Iadecola C, Gupta A, Kamel H (2017) Neutrophil-lymphocyte ratio and perihematomal edema growth in intracerebral hemorrhage. Stroke 48(9):2589–2592
22. Lattanzi S, Cagnetti C, Provinciali L, Silvestrini M (2017) Neutrophil-to-lymphocyte ratio and neurological deterioration following acute cerebral hemorrhage. Oncotarget 8(34):57489–57494. https://doi.org/10.18632/oncotarget.15423
23. Zhou D, Fan Y, Wan Z, Wen W, Wang X, Zhou J, Chen T, Yuan Z (2016) Platelet-to-lymphocyte ratio improves the predictive power of GRACE risk score for long-term cardiovascular events in patients with acute coronary syndrome. Cardiology 134(1):39–46. https://doi.org/10.1159/000442939
24. Chen N, Li W, Huang K, Yang W, Huang L, Cong T, Li Q, Qiu M (2017) Increased platelet-lymphocyte ratio closely relates to inferior clinical features and worse long-term survival in both resected and metastatic colorectal cancer: an updated systematic review and meta-analysis of 24 studies. Oncotarget 8(19):32356–32369. https://doi.org/10.18632/oncotarget.16020
25. Ozcan Cetin EH, Cetin MS, Canpolat U, Akdi A, Aras D, Temizhan A, Aydogdu S (2017) Platelet-to-lymphocyte ratio as a novel marker of in-hospital and long-term adverse outcomes among patients with acute pulmonary embolism: a single center large-scale study. Thromb Res 150:33–40. https://doi.org/10.1016/j.thromres.2016.12.006
26. Elhechmi YZ, Hassouna M, Cherif MA, Ben Kaddour R, Sedghiani I, Jerbi Z (2017) Prognostic value of serum C-reactive protein in spontaneous intracerebral hemorrhage: when should we take the sample? J Stroke Cerebrovasc Dis 26(5):1007–1012. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.11.129
27. Di Napoli M, Slevin M, Popa-Wagner A, Singh P, Lattanzi S, Divani AA (2018) Monomeric C-Reactive Protein and Cerebral Hemorrhage: From Bench to Bedside. Front Immunol 9:1921. https://doi.org/10.3389/fimmu.2018.01921
28. Béjot Y, Aboa-Eboulé C, Hervieu M, Jacquin A, Osseby G-V, Rouaud O, Giroud M (2012) The deleterious effect of admission hyperglycemia on survival and functional outcome in patients with intracerebral hemorrhage. Stroke 43(1):243–245
29. Koga M, Yamagami H, Okuda S, Okada Y, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Hasegawa Y, Kario K (2015) Blood glucose levels during the initial 72 h and 3-month functional outcomes in acute intracerebral hemorrhage: The SAMURAI–ICH study. J Neurol Sci 350(1–2):75–78
30. Zhang J, Cai L, Song Y, Shan B, He M, Ren Q, Chen C, Liu Z, Zeng Y, Xu J (2017) Prognostic role of neutrophil lymphocyte ratio in patients with spontaneous intracerebral hemorrhage. Oncotarget 8(44):77752
31. Jafari M, Di Napoli M, Lattanzi S, Mayer SA, Bachour S, Bershad EM, Damani R, Datta YH, Divani AA (2019) Serum magnesium level and hematoma expansion in patients with intracerebral hemorrhage. J Neurol Sci 398:39–44. https://doi.org/10.1016/j.jns.2019.01.027
32. Mahmoudi J, Majdi A, Lattanzi S, Di Napoli M, Bershad EM, Rodrigues CMP, Divani AA (2018) Imidazoline Receptor Agonists for Managing Hypertension May Hold Promise for Treatment of Intracerebral Hemorrhage. Curr Mol Med 18(4):241–251. https://doi.org/10.2174/1566524018666180926163712
33. Lattanzi S, Cagnetti C, Rinaldi C, Angelocola S, Provinciali L, Silvestrini M (2018) Neutrophil-to-lymphocyte ratio improves outcome prediction of acute intracerebral hemorrhage. J Neurol Sci 387:98–102. https://doi.org/10.1016/j.jns.2018.01.038
34. Lattanzi S, Brigo F, Trinka E, Cagnetti C, Di Napoli M, Silvestrini M (2019) Neutrophil-to-lymphocyte ratio in acute cerebral hemorrhage: a system review. Transl Stroke Res 10(2):137–145. https://doi.org/10.1007/s12975-018-0649-4

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