Neutrophil-to-Lymphocyte Ratio Is an Independent Predictor for In-Hospital Mortality in Spontaneous Intracerebral Hemorrhage

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Keywords

Intracerebral hemorrhage · Neutrophil-to-lymphocyte ratio · Inflammation · In-hospital mortality

Abstract

Background and Purpose: Stroke-associated immunosuppression and inflammation are increasingly recognized as factors that trigger infections and thus, potentially influence the outcome after stroke. Several studies demonstrated that elevated neutrophil-to-lymphocyte ratio (NLR) is a significant predictor of adverse outcomes in patients with ischemic stroke. However, little is known about the impact of NLR on short-term mortality in intracerebral hemorrhage (ICH).

Methods: This observational study included 855 consecutive ICH-patients. Patient demographics, clinical, laboratory, and in-hospital measures as well as neuroradiological data were retrieved from institutional databases. Functional 3-months-outcome was assessed and categorized as favorable (modified Rankin Scale [mRS] 0–3) and unfavorable (mRS 4–6). We (i) studied the natural course of NLR in ICH, (ii) analyzed parameters associated with NLR on admission (NLROA), and (iii) evaluated the clinical impact of NLR on mortality and functional outcome. **Results:** The median NLROA of the entire cohort was 4.66 and it remained stable during the entire hospital stay. Patients with NLR ≥ 4.66 showed significant associations with poorer neurological status (National Institute of

Health Stroke Scale [NIHSS] 18 [9–32] vs. 10 [4–21]; $p < 0.001$), larger hematoma volume on admission (17.6 [6.9–47.7] vs. 10.6 [3.8–31.7] mL; $p = 0.001$), and more frequently unfavorable outcome (mRS 4–6 at 3 months: 317/427 [74.2%] vs. 275/428 [64.3%]; $p = 0.002$). Patients with an NLR under the 25th percentile (NLR < 2.606) – compared to patients with NLR > 2.606 – presented with a better clinical status (NIHSS 12 [5–21] vs. 15 [6–28]; $p = 0.005$), lower hematoma volumes on admission (10.6 [3.6–30.1] vs. 15.1 [5.7–42.3] mL; $p = 0.004$) and showed a better functional outcome (3 months mRS 0–3: 82/214 [38.3%] vs. 185/641 [28.9%]; $p = 0.009$). Patients associated with high NLR (≥ 8.508 = above 75th-percentile) showed the worst neurological status on admission (NIHSS 21 [12–32] vs. 12 [5–23]; $p < 0.001$), larger hematoma volumes (21.0 [8.6–48.8] vs. 12.2 [4.1–34.9] mL; $p < 0.001$), and higher proportions of unfavorable functional outcome at 3 months (mRS 4–6: 173/214 vs. 418/641; $p < 0.001$). Further, NLR was linked to more frequently occurring infectious complications (pneumonia 107/214 vs. 240/641; $p = 0.001$, sepsis: 78/214 vs. 116/641; $p < 0.001$), and increased c-reactive-protein levels on admission ($p < 0.001$; $R^2 = 0.064$). Adjusting for the above-mentioned baseline confounders, multivariable logistic analyses revealed independent associations of NLROA with in-hospital mortality (OR 0.967, 95% CI 0.939–0.997; $p = 0.029$). **Conclusions:** NLR represents an independent parameter associated with increased mortality in ICH patients. Stroke physicians should focus intensely on patients with increased NLR,

as these patients appear to represent a population at risk for infectious complications and increased short-mortality. Whether these patients with elevated NLR may benefit from a close monitoring and specially designed therapies should be investigated in future studies.

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Introduction

Inflammation plays an important role in cerebrovascular diseases [1–4], including intracerebral hemorrhage (ICH) [5–7] and is usually monitored using a variety of biochemical and hematological markers [8–12]. Neutrophil-to-lymphocyte ratio (NLR), calculated by the absolute neutrophil count divided by the absolute lymphocyte count, is increasingly recognized as a readily available and inexpensive biomarker for systemic inflammation [13]. NLR reflects the balance between innate (neutrophil granulocytes) and adaptive (lymphocytes) immune responses as neutrophil elevation and lymphocyte depletion indicate physiological stress [14, 15].

Recently, in some ICH-studies, NLR has been associated with clinical endpoints [2, 12, 16–19]. However, in ICH patients, little is known about the natural course of systemic inflammation during hospital stay and whether NLR is associated with short-term mortality. This study for the first time investigated (i) the course of NLR, (ii) parameters associated with NLR, and (iii) the clinical impact of NLR on mortality and functional outcome after ICH.

Methods

Patient Selection

We analyzed all consecutive patients with spontaneous ICH admitted to the Department of Neurology, University Hospital Erlangen, Germany, between 2006 and 2014 ($n = 960$). By definition, we excluded secondary ICH etiologies, that is, ICH related to trauma, tumor, arteriovenous malformation, central venous thrombosis, subarachnoid hemorrhage or thrombolysis, as previously defined [20]. We did not include patients receiving permanent immunomodulatory treatments prior to admission, for example, consisting of corticosteroids, methotrexate, other cytostatic drugs and biologicals (monoclonal antibodies) and excluded all individuals with hematological, autoimmune, or infectious diseases. As 105 patients had no follow-up data, or refused consent, 855 patients participated in the final analysis.

Parameter Acquisition

As described previously [21], we retrieved data of all patients from our institutional prospective database. We reviewed data for demographics, prior medical history, imaging, and in-hospital pa-

rameters (Glasgow Coma Scale [GCS], National Institute of Health Stroke Scale [NIHSS], ICH-score, blood pressure, mechanical ventilation, length of stay, external ventricular drainage, diagnosis of pneumonia, urinary tract infection and sepsis, as defined elsewhere) [22–25].

Laboratory parameters were retrieved from our institutional database. We investigated NLR that was obtained immediately upon admission (NLROA) and subsequently during hospital stay in the morning (NLR days 1, 2, 3, 5, 7, 10, and 14). However, in cases of infections and need of frequent blood controls, we did not consider this additional blood work taken during other times of the day to avoid confounding. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count [5, 13] and average values for healthy controls ($NLR = 2.24$) were defined according to representative samples [26]. We chose to use a median split and 25th/75th percentile quartiles to categorize our ICH-patients.

We assessed patients' characteristics, for example, history of stroke, cardiovascular comorbidity, nicotine or alcohol abuse, using standardized mailed questionnaires. Semi-quantitative phone interviews were conducted – performed by physicians trained and certified for data collection on disability and quality of life – with patients or their closest relatives if the questionnaire was not returned within 2–4 weeks [21]. We contacted primary care physicians only in cases of insufficient data retrieval.

Outcome Measures

We obtained data on mortality and functional outcome as described above using the modified Rankin Scale (mRS) [27]. Functional outcome was evaluated using the mRS on day 90 after ICH onset. Favorable outcome was defined as mRS 0–3 and unfavorable outcome as mRS 4–6.

Imaging

As described previously [21], we diagnosed ICH by CT (SOMATOM Volume Zoom or SOMATOM Definition AS+, Siemens Healthcare GmbH, Forchheim/Germany) or MRI (Siemens Magnetom Aera, 1.5T, Siemens Healthcare GmbH, Erlangen/Germany). Two neuroradiologists (H.L. and P.H.) blinded to clinical data reviewed the scans independently and in cases of discrepancies made a second consensus analysis. We calculated ICH volume according to the ABC/2-formula and ABC/3-formula in irregularly shaped ICH [28, 29]. An increase in volume >33% upon follow-up was determined as hematoma enlargement [30]. Using the Graeb score summation, we scored the amount of intraventricular hematoma (IVH) [31].

Statistical Analysis

We used the statistical software package SPSS 20.0 (IBM Analytics; www.spss etc.). The significance level was set at $\alpha = 0.05$ two-sided. We used the Kolmogorov–Smirnov test to determine the distribution of data. Data compared with normal distribution using the Student t test are presented as mean $\pm$ SD. Continuous variables without normal distribution were analyzed using the Mann–Whitney U test and obtained as median (50th) values and interquartile ranges (25th/75th). Categorical variables were presented as frequency and percentage. We used the Pearson chi square and the Fisher's exact tests to compare frequency distributions of categorized variables between patients with median split and 25th/75th-percentile NLROA. To identify parameters inde-

Fig. 1. Course of neutrophile-to-lymphocyte ratio within 14 days after admission.

pendently associated with outcome, we developed step-wise forward inclusion multivariate logistic regression models including parameters showing a statistical trend ($p < 0.1$) in univariate testing.

Results

NLR over Time – Prevalence, Related Factors, and Outcome

The median NLR of the entire cohort was 4.66 on admission; the nadir occurred at day 5 (NLR = 4.65; Fig. 1). Patients with an NLR ≥ 4.66 , compared to patients with an NLR < 4.66 on admission, presented with higher NIHSS (18 [9–32] vs. 10 [4–21]; $p < 0.001$), larger hematoma volumes on admission (17.6 [6.9–47.7] vs. 10.6 [3.8–31.7] mL; $p < 0.001$) and more frequent IVH (258/427 [60.4%] vs. 167/428 [39.0%]; $p < 0.001$), more frequently developing pneumonia (195/427 [45.7%] vs. 150/428 [35.1%]; $p = 0.002$) and sepsis (117/427 [27.4%] vs. 77/428 [18.0%]; $p = 0.001$), necessity of ventilation (238/427 [55.7%] vs. 150/428 [35.1%]; $p < 0.001$), and increased rates of external ventricular drain placement (159/428 [37.2%] vs. 100/427 [23.4%]; $p < 0.001$; Table 1). Both mortality (178/427 [41.7%] vs. 127/428 [29.7%]; $p < 0.001$) and the proportion of patients with unfavorable functional outcome at 3 months (317/427 [74.2%] vs. 275/428 [64.3%]; $p = 0.002$) were significantly higher in patients with NLR ≥ 4.66 (Fig. 2).

Multivariable logistic regression models were performed to adjust for baseline confounders and to study possible independent effects of NLROA. NLROA was significantly associated with in-hospital mortality (NLROA: OR 0.967 [95% CI 0.939–0.997]; $p = 0.029$; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000468996) and showed a statistical trend on 3-month mortality (NLROA: OR 0.974 [95% CI 0.945–1.004]; $p = 0.087$; online suppl. Table 2). In contrast to published results [6], we did not identify NLR as an independent variable for unfavorable functional outcome at 3 months (NLROA: OR 0.983 [95% CI 0.939–1.029]; $p = 0.453$; online suppl. Table 3). NLROA showed a statistical trend to be independently associated with development of a sepsis (NLROA: OR 1.028 [95% CI 0.998–1.059]; $p < 0.071$; online suppl. Table 4) and there were significant associations of NLROA and C-reactive protein (CRP) concentrations (mg/L) on admission ($p < 0.001$, $R^2 = 0.064$; Fig. 3).

Clinical Significance of Increased and Decreased NLR

Given an average definition (NLR = 2.24) according to a nationally representative sample for healthy controls [26], we compared patients with an NLR under the 25th-percentile (NLR < 2.606) to those with an NLR ≥ 2.606 , and patients with NLR above the 75th-percentile (NLR ≥ 8.508) to patients with NLR < 8.508 . Out of 855 patients, 214 had an NLR < 2.606 (Table 2). These patients present-

Table 1. Demographic, baseline, neuroradiological, and laboratory data for all ICH patients with an NLR higher or lower than 4.66

Spontaneous ICH (<i>n</i> = 855)	NLR on admission ≥4.66 (<i>n</i> = 427)	NLR on admission <4.66 (<i>n</i> = 428)	<i>p</i> value
Age, years [‡]	72.5 (61–80)	71 (62–78)	0.412
Gender, female*	208 (48.7)	190 (44.4)	0.206
Prior medical history			
Pre-mRS [‡]	1 (0–2)	0 (0–1)	0.029
Hypertension*	359 (84.1)	346 (80.8)	0.248
Diabetes*	110 (25.8)	118 (27.6)	0.549
Dyslipidemia*	118 (27.8)	163 (38.1)	0.001
Ischemic stroke*	79 (18.5)	78 (18.2)	0.920
Hemorrhagic stroke*	36 (8.4)	49 (11.5)	0.141
Cardiac event*	59 (13.8)	63 (14.7)	0.708
Alcohol abuse*	92 (21.5)	80 (18.7)	0.299
Smoking*	140 (32.8)	138 (32.2)	0.862
Antiplatelet use*	125 (29.3)	142 (33.2)	0.218
On admission status			
NIHSS [‡]	18 (9–32)	10 (4–21)	<0.001
GCS [‡]	11 (3–14)	14 (9–15)	<0.001
ICH-score [‡]	2 (1–4)	1 (0–3)	<0.001
MAP, mm Hg [†]	114.3±24.1	119.6±24.2	0.032
Neuroradiological data			
Location; basalganglia*	189 (44.2)	195 (45.6)	0.699
Location; lobar*	190 (44.5)	189 (44.2)	0.920
Location; brainstem*	19 (4.5)	19 (4.4)	0.998
Location; cerebellar*	29 (6.8)	27 (6.3)	0.777
ICH volume, cm ^{3‡}	17.6 (6.9–47.7)	10.6 (3.8–31.7)	<0.001
IVH*	258 (60.4)	167 (39.0)	<0.001
Graeb score [‡]	2 (0–6)	0 (0–3)	<0.001
Hematoma growth*	36 (8.4)	59 (13.8)	0.013
Midline shift, mm [‡]	3 (0–8)	0 (0–5)	<0.001
Laboratory values on admission			
Hemoglobin, mmol/L [‡]	13.6 (12.2–14.9)	13.8 (12.7–15.0)	0.030
Hematocrit [‡]	39.4 (35.5–42.8)	40.1 (37.2–43.3)	0.004
Leucocytes, 10 ⁹ /L [‡]	10.8 (8.6–13.4)	7.8 (6.3–9.4)	<0.001
Thrombocytes, 10 ⁹ /L [‡]	218.0 (176.0–265.0)	222.0 (181.0–262.5)	0.910
Granulocytes, 10 ⁹ /L [‡]	9.1 (7.1–11.4)	4.8 (3.7–6.4)	<0.001
Lymphocytes, 10 ⁹ /L [‡]	1.0 (0.7–1.3)	2.0 (1.5–2.6)	<0.001
Monocytes, 10 ⁹ /L [‡]	0.6 (0.4–0.9)	0.7 (0.5–0.8)	0.025
CRP, mg/L [‡]	4.4 (2.0–11.0)	3.0 (1.8–7.0)	<0.001
In-hospital measures			
Mechanical ventilation*	238 (55.7)	150 (35.1)	<0.001
Duration of ventilation, days [‡]	1 (0–9)	0 (0–2)	<0.001
Pneumonia*	195 (45.7)	150 (35.1)	0.002
Sepsis*	117 (27.4)	77 (18.0)	0.001
Urinary tract infection*	48 (11.2)	35 (8.2)	0.130
External ventricular drain*	159 (37.2)	100 (23.4)	<0.001

Values are * *n* (%), [‡] median (interquartile range), or [†] mean ± SD. Bold values are significant.

ed with a better clinical status (NIHSS 12 [5–21] vs. 15 [6–28]; *p* < 0.005), and imaging (hematoma volumes 10.6 [3.6–30.1] vs. 15.1 [5.7–42.3] mL; *p* < 0.004) showed less infectious complications (pneumonia: 76/214 [35.5%] vs. 270/641 [42.1%]; *p* = 0.088 and sepsis: 35/214 [16.4%] vs. 162/641 [25.3%]; *p* = 0.007), required less mechanical

ventilation (73/214 [34.1%] vs. 316/641 [49.3%]; *p* < 0.001) and external ventricular drain placement (50/214 [23.3%] vs. 202/641 [31.5%]; *p* = 0.003), as compared to patients with NLR ≥2.606. Functional outcome was better in patients presenting with low NLR (<2.606) compared to those with higher NLR (mRS 0–3: 82/214 [38.3%] vs.

Fig. 2. The distribution of the modified Rankin Scale (mRS; 3-month-outcome dichotomized into mRS 0–3 vs. 4–6) for patients with a median neutrophile-to-lymphocyte ratio (NLR) on admission <4.66 and ≥ 4.66 .

185/641 [28.9%]; $p = 0.009$). However, in-hospital mortality and mRS on discharge did not differ significantly among both groups (Table 2).

Of the 855 patients, 214 showed an $\text{NLR} \geq 8.508$ (Table 3). These patients had an impaired neurological status on admission (NIHSS 20.5 [12–32] vs. 12 [5–23]; $p < 0.001$; GCS 10 [3–13] vs. 13 [7–15]; $p < 0.001$) as well as increased hematoma volumes (21.0 [8.6–48.8] vs. 12.2 [4.1–34.9] mL; $p < 0.001$; Table 3). Patients with $\text{NLR} \geq 8.508$ experienced significantly more often infectious complications (pneumonia 107/214 [50.0%] vs. 240/641 [37.4%]; $p = 0.001$ and sepsis: 78/214 [36.5%] vs. 116/641 [18.1%]; $p < 0.001$), required significantly more often mechanical ventilation and external ventricular drain (132/214 [61.7%] vs. 258/641 [40.3%]; and 88/214 [41.0%] vs. 172/641 [26.8%]; both, $p < 0.001$). Both in-hospital mortality (61/214 [28.5%] vs. 136/641 [21.2%]; $p = 0.041$) and the proportion of patients with unfavorable functional outcome (mRS 4–6: 173/214 [80.8%] vs. 418/641 [65.2%]; $p < 0.001$) and 3-month mortality (95/214 [44.4%] vs. 211/641 [33.0%]; $p = 0.002$) were significantly higher in patients with $\text{NLR} \geq 8.508$ (Table 3).

Discussion

This study systematically investigated the natural course and clinical impact of NLR in a large cohort of ICH patients. As key findings, we observed increased baseline NLR levels compared to healthy individuals [26]. Further, an elevated NLR was linked to unfavorable baseline clinical and radiological parameters, increased infectious

Fig. 3. Scatter plot of neutrophile-to-lymphocyte ratio and C-reactive protein (CRP; mg/L) on admission ($n = 766$, $R^2 = 0.064$; $p < 0.001$).

complications, as well as elevated c-reactive-protein levels on admission translating into worse clinical endpoints, notably an independent association of NLROA with in-hospital mortality.

Our results are in line with previous data indicating that an elevated NLR is associated with early neurological deterioration [32] as well as increased short-term mortality rates [16]. Consistent with recent publications, in-

Table 2. Demographic, baseline, neuroradiological, and laboratory data for all ICH patients with an NLR lower or higher than 2.606

Spontaneous ICH (<i>n</i> = 855)	NLR on admission <2.606 (<i>n</i> = 214)	NLR on admission ≥2.606 (<i>n</i> = 641)	<i>p</i> value
Age, years [‡]	71 (63–78)	72 (61–79)	0.584
Gender, female*	90 (42.1)	307 (47.9)	0.138
Prior medical history			
Pre-mRS [‡]	0 (0–1)	1 (0–2)	0.002
Hypertension*	170 (79.4)	530 (82.7)	0.286
Diabetes*	60 (28.0)	165 (25.7)	0.507
Dyslipidemia*	84 (39.3)	195 (30.4)	0.017
Ischemic stroke*	44 (20.6)	112 (17.5)	0.310
Hemorrhagic stroke*	26 (12.1)	59 (9.2)	0.213
Cardiac event*	38 (17.8)	84 (13.1)	<i>0.092</i>
Alcohol abuse*	36 (16.8)	135 (21.1)	0.179
Smoking*	75 (35.1)	200 (31.2)	0.296
Antiplatelet use*	76 (35.5)	193 (30.1)	0.141
On admission status			
NIHSS [‡]	12 (5–21)	15 (6–28)	0.005
GCS [‡]	13 (9–15)	12 (3–15)	0.001
ICH-score [‡]	1 (0–3)	2 (1–3)	0.002
MAP, mm Hg [†]	122.6±23.7	114.9±24.4	0.008
Neuroradiological data			
Location; basalganglia*	112 (52.3)	270 (42.1)	0.009
Location; lobar*	77 (36.0)	300 (46.8)	0.006
Location; brainstem*	13 (6.1)	26 (4.1)	0.221
Location; cerebellar*	12 (5.6)	44 (6.8)	0.532
ICH volume, cm ^{3‡}	10.6 (3.6–30.1)	15.1 (5.7–42.3)	0.004
IVH*	89 (41.6)	336 (52.4)	0.006
Graeb score [‡]	0 (0–4)	1 (0–5)	0.007
Hematoma growth*	36 (16.8)	59 (9.2)	0.002
Midline shift, mm [‡]	0 (0–5)	2 (0–7)	0.031
Laboratory values on admission			
Hemoglobin, mmol/L [‡]	14.1 (12.9–15.2)	13.6 (12.3–14.9)	0.005
Hematocrit [‡]	40.7 (37.7–43.6)	39.6 (35.8–42.8)	0.003
Leucocytes, 10 ⁹ /L [‡]	7.4 (6.1–8.7)	9.8 (7.8–12.5)	<0.001
Thrombocytes, 10 ⁹ /L [‡]	220 (182–259)	220 (176–265)	0.812
Granulocytes, 10 ⁹ /L [‡]	4.1 (3.3–5.0)	7.9 (5.9–10.3)	<0.001
Lymphocytes, 10 ⁹ /L [‡]	2.3 (1.9–3.1)	1.2 (0.8–1.6)	<0.001
Monocytes, 10 ⁹ /L [‡]	0.68 (0.52–0.82)	0.63 (0.47–0.86)	0.162
CRP, mg/L [‡]	2.4 (1.5–5.7)	4.1 (2.0–10.4)	<0.001
In-hospital measures			
Mechanical ventilation*	73 (34.1)	316 (49.3)	<0.001
Duration of ventilation, days [‡]	0 (0–3)	0 (0–7)	0.003
Pneumonia*	76 (35.5)	270 (42.1)	<i>0.088</i>
Sepsis*	35 (16.4)	162 (25.3)	0.007
Urinary tract infection*	16 (7.5)	72 (11.2)	0.118
External ventricular drain*	50 (23.3)	202 (31.5)	0.003
Outcome parameters			
mRS discharge [‡]	5 (3–6)	5 (3–5)	0.950
mRS (3 months) [‡]	4 (2–6)	5 (3–6)	0.007
In-hospital mortality*	46 (21.5)	154 (24.0)	0.450
Favorable outcome (mRS 0–3) 3 months*	82 (38.3)	185 (28.9)	0.009
Non-favorable outcome (mRS 4–6) 3 months*	132 (61.6)	456 (71.1)	0.009
3-Month mortality*	63 (29.4)	244 (38.1)	0.023

Values are * *n* (%), [‡] median (interquartile range), or [†] mean ± SD. Bold values are significant, italic values show a statistical trend (i.e., *p* < 0.1).

Table 3. Demographic, baseline, neuroradiological, and laboratory data for all ICH patients with an NLR higher or lower than 8.508

Spontaneous ICH (<i>n</i> = 855)	NLR on admission ≥8.508 (<i>n</i> = 214)	NLR on admission <8.508 (<i>n</i> = 641)	<i>p</i> value
Age, years [‡]	73 (61–80)	71 (62–79)	0.516
Gender, female*	104 (48.6)	292 (45.6)	0.439
Prior medical history			
Pre-mRS [‡]	1 (0–3)	0 (0–2)	0.012
Hypertension*	187 (87.4)	513 (80.0)	0.016
Diabetes*	57 (26.6)	161 (25.1)	0.663
Dyslipidemia*	57 (26.6)	220 (34.3)	0.038
Ischemic stroke*	41 (19.2)	117 (18.3)	0.764
Hemorrhagic stroke*	21 (9.8)	64 (10.0)	0.920
Cardiac event*	32 (14.9)	90 (14.0)	0.724
Alcohol abuse*	56 (26.2)	117 (18.3)	0.013
Smoking*	73 (34.1)	205 (32.0)	0.566
Antiplatelet use*	62 (29.0)	207 (32.3)	0.365
On admission status			
NIHSS [‡]	21 (12–32)	12 (5–23)	<0.001
GCS [‡]	10 (3–13)	13 (7–15)	<0.001
ICH-score [‡]	3 (1–4)	2 (1–3)	<0.001
MAP [†]	114.2±26.9	117.8±23.5	0.258
Neuroradiological data			
Location; basalganglia*	93 (43.5)	290 (45.2)	0.646
Location; lobar*	99 (46.2)	280 (43.7)	0.512
Location; brainstem*	8 (3.7)	31 (4.8)	0.507
Location; cerebellar*	14 (6.5)	43 (6.7)	0.920
ICH volume, cm ^{3‡}	21.0 (8.6–48.8)	12.2 (4.1–34.9)	<0.001
IVH*	141 (65.9)	285 (44.5)	<0.001
Graeb score [‡]	3 (0–6)	0 (0–4)	<0.001
Hematoma growth*	14 (6.5)	79 (12.3)	0.019
Midline shift, mm [‡]	5 (0–8)	0 (0–5.5)	<0.001
Laboratory values on admission			
Hemoglobin, mmol/L [‡]	13.6 (12.0–14.8)	13.7 (12.6–15.0)	0.019
Hematocrit [‡]	39.0 (35.1–42.8)	40.0 (36.8–43.1)	0.008
Leucocytes, 10 ⁹ /L [‡]	11.9 (9.6–14.9)	8.4 (6.7–10.4)	<0.001
Thrombocytes, 10 ⁹ /L [‡]	215 (176–258)	222 (179–265)	0.894
Granulocytes, 10 ⁹ /L [‡]	10.4 (8.4–13.2)	5.6 (4.2–7.7)	<0.001
Lymphocytes, 10 ⁹ /L [‡]	0.75 (0.6–1.0)	1.7 (1.3–2.2)	<0.001
Monocytes, 10 ⁹ /L [‡]	0.61 (0.43–0.94)	0.65 (0.49–0.83)	0.650
CRP, mg/L [‡]	4.7 (2.0–15)	3.3 (1.8–8.0)	<0.001
In-hospital measures			
Mechanical ventilation*	132 (61.7)	258 (40.3)	<0.001
Duration of ventilation, days [‡]	1 (0–12)	0 (0–3)	<0.001
Pneumonia*	107 (50.0)	240 (37.4)	0.001
Sepsis*	78 (36.5)	116 (18.1)	<0.001
Urinary tract infection*	24 (11.2)	60 (9.4)	0.431
External ventricular drain*	88 (41.0)	172 (26.8)	<0.001
Outcome parameters			
mRS discharge [‡]	5 (4–6)	4 (3–5)	<0.001
mRS (3 months) [‡]	5 (4–6)	4 (3–6)	<0.001
In-hospital mortality*	61 (28.5)	136 (21.2)	0.041
Favorable outcome (mRS 0–3) 3 months*	41 (19.2)	223 (34.8)	<0.001
Non-favorable outcome (mRS 4–6) 3 months*	173 (80.8)	418 (65.2)	<0.001
3-Month mortality*	95 (44.4)	211 (33.0)	0.002

Values are * *n* (%), [‡] median (interquartile range), or [†] mean ± SD. Bold values are significant.

flammation was significantly associated with unfavorable outcome [16, 33, 34]; however, we did not identify NLR as an independent predictor for outcome in ICH [6, 16], which is in line with data from INTERACT2 [18, 35]. Regarding functional outcome and its possible relation to hematoma enlargement, Morotti et al. [19] – contrary to this study – found associations of higher neutrophil counts with reduced risk of hematoma expansion. The authors linked their finding to the hypothesis that the inflammatory response may exert beneficial aspects during the hyperacute phase such that activated neutrophils exhibit a procoagulant effect so that coagulation may be improved and therefore early hematoma expansion reduced [19].

However, there may also be an association of neutrophils, and NLR ratio respectively, with inflammatory complications [33, 36–38]. As demonstrated earlier, initial neutrophil infiltration contributes also to secondary brain injury [39]. The resulting expression of inflammatory markers, for example, interleukin-6 [12] and various pro-inflammatory cytokines [11, 12, 36, 38] may lead to further cellular DNA damage. Apoptosis and functional deactivation of peripheral lymphocytes [34, 40] reflect an important – though impaired – role in host defense. This can predispose to infectious complications later during hospital stay, as shown in our study. As NLR is known to be useful for the diagnosis of bacterial infections in patients with fever [41], we showed significant associations of CRP concentrations and a trend to independent associations with sepsis.

Given the complex inflammatory process, there are various limitations of our study. This study lacks a prospective and multi-center design without specific blood sampling analyses. Regimens for diagnosis as well as treatment of infections have not been reported why the significance of reported associations may be weakened.

Although NLR did not significantly change among our ICH cohort during hospital stay, varying time points between stroke-onset, occurrence of infections and blood sampling may represent important potential confounders. However, excluding patients with elevated CRP levels on admission (>20 mg/L = twice the standard-level, and about 15% of our cohort) resulted in similar clinical endpoints (data not shown). Finally, we did not score for ICH etiologies, as there are probable associations between cerebral amyloid angiopathy and inflammation [42, 43]. Further, outcome analyses were based on self-reporting rather than on objectively blinded assessment. Although we accounted for statistical bias, findings of this study may still overestimate causal and clinical associations.

In conclusion, our data reveal increased baseline NLR levels in ICH, which is linked to unfavorable baseline parameters, increased infectious complications, and worse clinical endpoints. However, whether a close monitoring of specific subsets of ICH patients with increased NLR may result in beneficial outcome measures requires further investigations.

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