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REVIEW ARTICLE

Neutrophil-to-Lymphocyte Ratio in Acute Cerebral Hemorrhage: a System Review

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Abstract

Spontaneous intracerebral hemorrhage (ICH) accounts for approximately 10 to 30% of all acute cerebrovascular events, and it is the type of stroke associated with the highest rates of mortality and residual disability. The inflammatory response is early triggered by hematoma components and can enhance the damage within the hemorrhagic brain. Assessment of peripheral biomarkers of inflammation could contribute to increase knowledge about some of the mechanisms involved in the ICH-induced injury and yield information on the disease course. The neutrophil-to-lymphocyte ratio (NLR) integrates information on both the innate and adaptive compartments of the immunity and represents a reliable measure of the inflammatory burden. The aim of the current review is to highlight the available evidence about the relationships between the NLR and clinical outcome in patients with acute ICH and provide critical insights into the underlying pathophysiology. Since no therapy targeting ICH-induced primary injury has yielded conclusive benefits and ICH treatment remains mainly supportive within a framework of general critical care management, these findings could also contribute to identify new potential targets for neuroprotection and develop novel therapeutic strategies.

Keywords Cerebral hemorrhage · Stroke · Cerebrovascular disease · Inflammation · Neutrophil-to-lymphocyte ratio

Introduction

Spontaneous intracerebral hemorrhage (ICH) accounts for approximately 10 to 30% of all strokes and shows the highest rates of mortality and residual disability among survivors [1, 2]. Experimental models and clinical studies provided increasing evidence that inflammatory reactions are early triggered by hematoma components, enhance the damage within the hemorrhagic brain, and influence the patients' prognosis [3, 4]. Peripheral biomarkers may result from the inflammatory mechanisms involved in the ICH-induced injury and yield information on the disease course.

The neutrophil-to-lymphocyte ratio (NLR) has been proposed as an easy parameter to assess the individual inflammatory status [5]. It has proven its accuracy in predicting the outcome of patients with major cardiac events [6], ischemic stroke [7], cancers [8], sepsis, and infectious pathologies [9]. Recently, its predictive value has been also suggested in patients with ICH.

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The aim of this review is to summarize the available evidence about the relationships between the NLR and clinical outcome in patients with acute ICH, provide critical insights into the underlying pathophysiology, and suggest implications for clinical practice and future research. The most relevant studies on this topic were identified through MEDLINE (accessed by PubMed as of May 2018, week 3), using the following terms: "neutrophil lymphocyte ratio" and "stroke," "cerebral hemorrhage," "cerebral hematoma," "intracerebral hemorrhage," "intracerebral hematoma," "intracranial hemorrhage," or "intracranial hematoma." The reference lists of retrieved articles were reviewed to search for additional reports of relevant data. Prospective and retrospective studies were selected if NLR values and associations with clinical endpoints were reported and participants were diagnosed with acute ICH.

Neutrophil-to-Lymphocyte Ratio and Clinical Outcome Following Cerebral Hemorrhage: the Evidence from Clinical Studies

One hundred and two records were identified by database searching, of which 91 were excluded due to irrelevance (reviews, comments, unrelated to topic, unavailable data on clinical outcomes) (Fig. 1). Eleven studies, which assessed short- or long-term clinical outcomes as primary endpoints, i.e., early neurological deterioration, 30-day and in-hospital mortality, and 3-month death and disability, were included in the review (Table 1). The main characteristics of the patients enrolled in the studies are summarized in Table 2.

The relationship between the NLR and early neurological deterioration (ND) was investigated in a retrospective cohort study performed at a tertiary stroke center [10]. The patients who worsened during the first week had higher total white blood cells, higher absolute neutrophil count, lower absolute lymphocyte count, and higher NLR compared to those who did not deteriorate. The NLR was independently associated with ND and resulted in the best discriminating variable for the occurrence of the unfavorable outcome.

The association between the NLR values and 30-day fatality has been also investigated. Wang et al. described 224 patients admitted to the Emergency Department of the Jiading District Center Hospital, Shanghai, China within 24 h from ICH symptoms' onset over a 2-year period [11]. The NLR on the next morning following admission was significantly higher among patients who died than in those who survived, and resulted in an independent risk factor of 30-day mortality. The optimal NLR cut-off value to distinguish between survival and not-survival was 7.35. A validation study in an independent retrospective cohort of ICH patients confirmed the NLR above 7.35 as an independent predictor of poor short-term survival [12].

The same research team explored also the relationship between 1-week NLR trajectory and 30-day prognosis [13]. In a retrospective analysis of patients with acute ICH, the NLR values obtained at 24–48 h and 5–7 days after symptoms' onset were significantly higher in patients who died while remained relatively stable in those who survived. The early

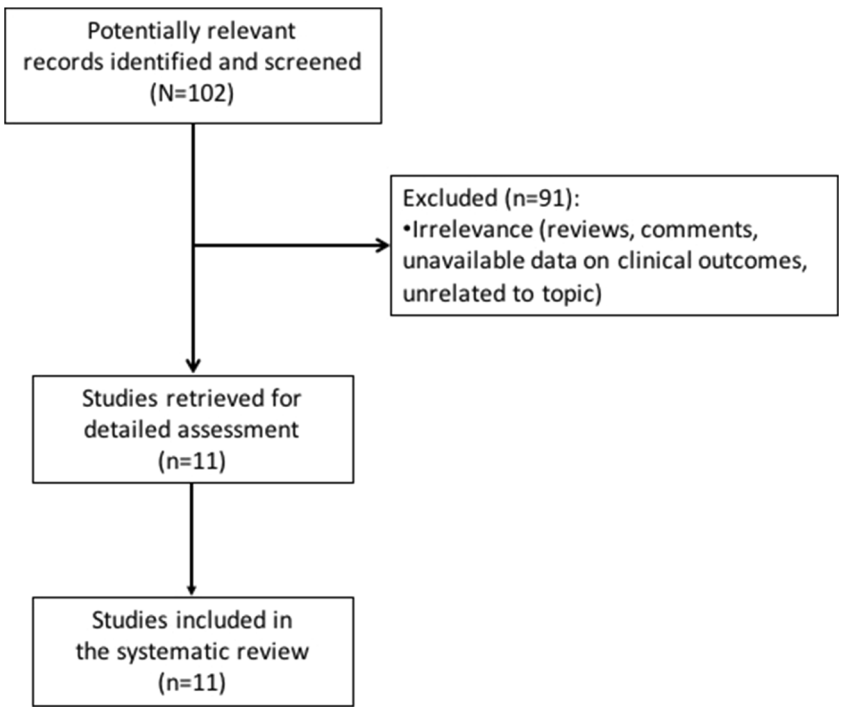

Fig. 1 Flow diagram of study selection process

Table 1 Synopsis of the studies

Study	Inclusion criteria	Exclusion criteria	Primary endpoint
Lattanzi et al., 2017 [10]	Patients with stroke syndrome due to acute spontaneous ICH, admission within 24 h from symptom onset	Isolated IVH, hemorrhage secondary to brain tumor, dural venous sinus thrombosis, ruptured aneurysm or arteriovenous malformation, immunomodulatory or immunosuppressive treatment	[a]Neurological deterioration
Wang et al., 2016 [11]	Patients (≥ 18 years) with a diagnosis of ICH verified by CT scans, admission to hospital within 24 h after ICH	Hematologic disorders, immunosuppressant drugs, trauma, anticoagulants, history of infection within 2 weeks, history of stroke within 6 months, history of malignancy	30-day mortality
Wang et al., 2018 [12]	Patients (≥ 18 years) with a diagnosis of ICH verified by CT scans, admission to hospital within 24 h after ICH	Hematologic disorders, immunosuppressant drugs, anticoagulants, history of infection within 2 weeks, stroke history within 6 months, history of malignancy	30-day mortality
Wang et al., 2018 [13]	Patients (≥ 18 years) with a diagnosis of ICH verified by CT scans, admission to hospital within 24 h after ICH	Hematologic disorders, immunosuppressant drugs, anticoagulants, history of infection within 2 weeks, stroke history within 6 months, history of malignancy	30-day mortality
Gökhan et al., 2013 [14]	Patients with stroke or TIA proven by clinical picture, CT, or MRI scans	Trauma, surgery, neoplasm, active infection, immunosuppressive agent use, hematologic or inflammatory diseases, severe hepatic and renal disease, acute metabolic disease/intoxication, previous stroke, and TIA	30-day mortality
Lattanzi et al., 2018 [15]	Patients with stroke syndrome due to acute spontaneous ICH, admission within 24 h from symptom onset	Isolated IVH, hemorrhage secondary to brain tumor, dural venous sinus thrombosis, ruptured aneurysm or arteriovenous malformation, immunomodulatory or immunosuppressive treatment	30-day outcome. Poor outcome: death or major disability (mRS score ≥ 3)
Giede-Jeppe et al., 2017 [16]	Patients with acute spontaneous ICH	Trauma, tumor, arteriovenous malformation, central venous thrombosis, subarachnoid hemorrhage or thrombolysis, immunomodulatory treatments, hematological, autoimmune, or infectious diseases	In-hospital mortality, 3-month outcome. Poor outcome: death or severe disability (mRS score > 3)
Tao et al., 2017 [17]	Patients (> 18 years) with a diagnosis of ICH confirmed by CT or MRI scans, admission within 24 h from onset of symptoms	Acute/chronic infection, systemic inflammatory disease, neoplasm, autoimmune diseases; dementia or mRS ≥ 3 before stroke; coagulation disorders; secondary hemorrhage due to trauma, tumor, aneurysm, vascular structural abnormalities and hemorrhagic transformation of cerebral infarct; severe renal dysfunction	3-month outcome. Poor outcome: death or moderate to severe disability (mRS score > 2)
Lattanzi et al., 2016 [18]	Patients with stroke syndrome due to acute spontaneous ICH, within 24 h from symptom onset	Isolated IVH, hemorrhage secondary to brain tumor, dural venous sinus thrombosis, ruptured aneurysm or arteriovenous malformation, immunomodulatory or immunosuppressive treatment	3-month outcome. Poor outcome: death or major disability (mRS score ≥ 3)
Sun et al., 2017 [19]	Patients with acute ICH confirmed by CT scans	Trauma, brain tumor, hemorrhagic transformation of ischemic stroke, vascular cerebral malformations	3-month outcome. Poor outcome: death or major disability (mRS score ≥ 3)
Zhang et al., 2018 [20]	Patients (> 18 years) with primary brainstem hemorrhage, admission and diagnostic/laboratory tests within 24 h from symptom onset	Trauma, brain tumor or aneurysm, stroke within 6 months, acute infection within 2 weeks, neoplasm, uremia, liver cirrhosis, autoimmune disease, chronic heart disease, severe renal dysfunction, chronic lung disease, immunosuppressive drugs or anticoagulants, surgical hematoma treatment.	3-month outcome. Poor outcome: death, persistent vegetative state or severe disability (GOS ≤ 3)

GOS Glasgow Outcome Scale; *ICH* intracerebral haemorrhage, *IVH* intraventricular hemorrhage, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *TIA* transient ischemic attack.

[a] Neurological deterioration was defined as ≥ 4 point increase in the NIHSS score or ≥ 2 point decrease in the GCS score or death from the time of admission to 7 days post-ICH

Table 2 Characteristics of the included patients

Study	Patients, number	Age, years	Male, %	Clinical severity	ICH volume, mL	NLR values	Time onset to sample
Lattanzi et al., 2017 [10]	192	66.9 ± 12.5	64.1	NIHSS score 9 (6–14)	8.1 (3.5–16.0)	5.16 ± 4.57	17.3 h (15.7–19.3)
Wang et al., 2016 [11]	224	67.97 ± 13.75	62.9	GCS score 12.64 ± 3.49	14.94 ± 14.13	2.47 ± 1.81 (admission); 6.34 ± 5.85 (next morning)	175.98 ± 101.97 min
Wang et al., 2018 [12]	181	65.8 ± 14.3	61.9	GCS score 11.5 ± 4.2	23.8 ± 35.2	8.7 ± 8.6	14.8 ± 6.9 h
Wang et al., 2018 [13]	275	27–94	75.3	[a]GCS score 8 (5–11)/14 (12–15)	[a]45.6 (20–80)/ 8.9 (3.3–22.4)	3.2 (1.8–6.2) (admission)	[a]6.3 (2.7–11.6)/5.0 h (2.0–15.1)
Gökhan et al., 2013 [14]	124	66.56 ± 11.86	51.6	NA	NA	5.02 ± 4.30	NA
Lattanzi et al., 2018 [15]	208	66.7 ± 12.4	63.5	NIHSS score 9 (6–14)	7.8 (3.3–15.1)	5.20 ± 4.45	17.2 h (15.4–18.8)
Giede-Jeppe et al., 2017 [16]	855	71.75	53.5	[b]NIHSS score 8–10	[b]10.6–17.6	4.66 (2.6–8.5)	NA
Tao et al., 2017 [17]	336	58.5 ± 13.0	64.3	GCS score 11 (7–13)	15.8 (6.8–32.4)	8.7 (4.3–14.7)	11.9 h (9.2–14.4)
Lattanzi et al., 2016 [18]	177	67.1 ± 12.51	64.4	NIHSS score 9 (6–14)	8.1 (3.5–16.0)	5.22 ± 5.04	17.3 h (15.8–19.0)
Sun et al., 2017 [19]	352	64.2 ± 13.8	66.5	[b]NIHSS score 6–11	[b]9.1–15.0	4.08 (2.78–7.85)	2.0–24.0 h
Zhang et al., 2018 [20]	225	53.20 ± 10.74	78.2	GCS score 10 (6–14)	5.4 (2.7–12.8)	7.1(4.4–9.1)	7 h (4–17)

Data are mean ± standard deviation, median (interquartile range), or range unless otherwise specified

GCS Glasgow Coma Scale, *NA* not available, *NIHSS* National Institutes of Health Stroke Scale, *NLR* neutrophil-to-lymphocyte ratio

[a] Values are reported according to 30-day outcome (death/survival)

[b] The range of the median values across the NLR quartiles is reported

increase of the NLR within the first week after hospitalization resulted in a risk factor for 30-day mortality, independently from the ICH severity.

Gökhan et al. studied 868 patients with acute cerebrovascular events, including strokes and transient ischemic attacks, admitted to the Diyarbakır Research and Education Hospital Emergency Service, Turkey between 2009 and 2011 [14]. In-hospital death occurred nearly in 20% of the cases, and the admission NLR values were significantly higher in dead than in surviving patients.

The 30-day functional status was the primary endpoint of a single-center retrospective study [15]. Among the patients hospitalized for stroke syndrome due to spontaneous ICH, the NLR was significantly associated with 30-day functional status and its addition to the modified ICH score, which is one of the most reliable prognostic model, improved the accuracy of outcome prediction by approximately 20%.

Finally, five studies investigated the relationship between the NLR and 3-month functional outcome [16–20]. Eight hundreds and fifty-five patients with spontaneous ICH were consecutively admitted to the Department of Neurology, University Hospital Erlangen, Germany, between 2006 and 2014 [16]. Patients with higher NLR values presented an increased risk of in-hospital, unfavorable 3-month outcome, and 3-month mortality.

Tao et al. retrospectively identified patients with spontaneous ICH admitted to the West China Hospital of Sichuan University from July 2010 to January 2013 [17]. Clinical outcome was assessed at 90 days using the modified Ranking scale by personnel blinded to laboratory values. Patients classified as having poor outcome presented higher NLR compared to cases with favorable clinical course. The NLR was significantly associated with 90-day status, and its predictive ability was better for death than for poor outcome.

The occurrence of death or major disability at 3 months was the primary endpoint of a retrospective study that included 177 patients within 24 h from onset [18]. Poor outcome patients had higher NLR compared to those with good functional status. The NLR was independently associated with outcome, and the optimal predictive threshold was set at 4.58.

Sun et al. prospectively identified patients with acute ICH admitted to the Second Affiliated Hospital of Soochow University in China from November 2011 to March 2014 [19]. Patients were grouped into quartiles according to admission NLR levels. Death or major disability occurred in 60.23% of the patients in the highest NLR quartile and in 36.78% of those in the lowest.

The predictive value of the NLR in ICHs selectively localized to the brainstem has been recently explored [20]. In-patients diagnosed with primary brainstem hemorrhage admitted at the West China Hospital between January 2012 and December 2016 were retrospectively identified. At 3 months, nearly half of the patients had unfavorable outcome, defined

as death, persistent vegetative state, or severe disability. The NLR was independently associated with the clinical outcome, and the optimal predictive cut-off point was set at 6.65.

The details of the findings of all included studies are provided in Table 3.

Neutrophil-to-Lymphocyte Ratio and Cerebral Hemorrhage: Looking Insight Pathophysiology

Converging evidence suggests that the NLR can be a reliable predictor of clinical outcome in patients with acute ICH. Different mechanisms can explain these findings from a pathophysiological point of view.

The inflammatory response begins immediately after the stroke onset. Hematoma components initiate inflammatory signaling via activation of microglia, which subsequently release pro-inflammatory cytokines and chemokines to favor peripheral inflammatory infiltration [4, 21]. Notably, neutrophils are the earliest leukocytes recruited from peripheral blood into the brain. Neutrophils are observed in and around the hematoma as early as 4 h after collagenase-induced ICH in animal models, peak at 2 to 3 days, and they almost disappear within the first week [21]. Peri-hematomal tissue obtained from patients with ICH confirmed that leukocyte infiltration occurs in less than 8 h and further increases within 1 day after the ICH onset [22].

Blood-derived inflammatory cells strongly contribute to the secondary brain injury following ICH. The neutrophil-induced neurotoxicity is related to a multitude of pathways, including the secretion of cytotoxic mediators and pro-inflammatory cytokines like TNF-α and IL-1b, the upregulation of matrix metalloproteinases, the excessive generation of reactive oxygen species, and the macrophage activation [23]. The ensuing increase of capillary permeability, blood-brain barrier breakdown, and cellular swelling can favor the hematoma growth and edema formation, raise the intracranial pressure, cause the cerebral tissue displacement and, thus, negatively affect stroke recovery [24–27]. Indeed, clinical studies demonstrated the early increase of peripheral neutrophils as an independent predictor of peri-hemorrhagic edema development, which is a radiologic marker for secondary injury following cerebral hematoma, and a risk factor of early neurological deterioration and poor ICH outcome [28–30]. The key role of neutrophils in the ICH pathophysiology is further strengthened by pre-clinical studies. In animal models, the selective neutrophil depletion prior to ICH decreased the astrocytic and microglial/macrophage response, the myelin fragmentation, and the axon damage in the peri-hematoma region and ameliorated the functional outcome [31, 32]. Similarly, the early inhibition of the neutrophil-derived matrix metalloproteinases after ICH provided neuroprotection against ICH-induced early brain injury [33, 34], decreased glial activation and neural apoptosis, reduced injury volume, and improved neurobehavioral recovery [35].

The interaction between brain and immunity is bidirectional, and acute injury of vulnerable areas within the central nervous system may have profound effects on the immune function. In the first days following a stroke, patients may develop a state of immunodepression as the result of increased levels of catecholamines and steroids. These changes in humoral and hormonal milieu derive from the hyper-activation of the sympathetic nervous system and hypothalamic-pituitary adrenal axis and can induce the apoptosis and functional deactivation of peripheral lymphocytes [36]. Signally, lymphocytes are major regulators of the immune system and key players of the cellular and humoral responses. They have a crucial role in the host defense against pathogens, and their loss reduces the immune competence and increases the vulnerability to infections. In experimental studies, post-stroke inhibition of adaptive immunity resulted in spontaneous bacterial infections, and low percentages of lymphocytes independently predicted the incidence of infections in ICH patients [16, 37, 38]. Remarkably, infectious complications can induce hyperthermia, increase cerebral metabolic demands, favor acidosis, hypoxia, electrolytic unbalance, and venous thrombosis [39–41], and they have been consistently associated with increased morbidity and mortality after ICH [42].

Since the strong relationships between the immune system and ICH pathophysiology, parameters that can reflect and synthesize the inflammatory response may relate to the disease course. In this respect, the NLR is a composite index with the merit to integrate information on both the innate and adaptive compartments of the immunity. In the acute stage of ICH, the NLR may reasonably represent a surrogate biomarker of the immune reactions triggered by cerebral hematoma at either local or systemic level and reflect at once the likelihood of secondary brain injury and vulnerability to post stroke complications. Accordingly, the early increase of the NLR values driven by neutrophils raise and/or lymphocyte reduction can result in the reliable prediction of the growth of peri-hemorrhagic edema [28], the risk of developing infections [16], and the occurrence of early neurological deterioration [10], short-term mortality [11–15], and adverse 3-month outcome [16–20].

Implications for Clinical Practice and Future Research

Prognostic models should help to stratify the risk of patients with ICH, design individual management, standardize communication among healthcare providers, and predict recovery

Table 3 Synthesis of the main findings

Study	Main Findings
Lattanzi et al, 2017 [10]	Fifty-four (28.1%) patients presented ND during the first week after ICH onset. The patients who worsened had higher NLR compared to those who did not experience ND (9.46 ± 5.80 versus 3.28 ± 1.98; $p < 0.001$). At logistic regression analysis after adjustment by age, sex, initial NIHSS score, baseline ICH volume, hematoma location, presence of IVH, hemorrhage, systolic and diastolic BP variability, the NLR was significantly associated with ND (OR 1.65, 95% CI 1.36–2.00; $p < 0.001$). At the ROC analysis, the NLR had an AUC of 0.888 (95% CI, 0.832–0.945). The Youden's index identified the best cut-off of NLR for ND at 5.46 (sensitivity 70.4%, specificity 90.6%, positive predictive value 74.5%, negative predictive value 88.7%, accuracy 84.9%).
Wang et al., 2016 [11]	The mortality rate during hospitalization was 11.6%. The NLR on the next morning following admission was significantly higher in patients who died than in those who survived (12.53 ± 9.33 versus 5.53 ± 4.68; $p < 0.001$). At multivariate logistic regression analysis, the NLR was independently associated with in-hospital death (OR 1.091, 95% CI 1.002–1.188; $p = 0.044$). The NLR had an AUC for death prediction of 0.762 (95% CI 0.649–0.875; $p < 0.001$). The optimal threshold to distinguish between survival and not-survival was 7.35 (sensitivity 69.2%, specificity 80.3%, accuracy 79.0%). The 30-day mortality rates were 31.6 and 4.8% ($p < 0.001$) in patients with NLR ≥ 7.35 and NLR < 7.35, respectively.
Wang et al., 2018 [12]	The 30-day mortality was 1.6, 15.0, and 41.7% in the lowest, middle, and highest tertile of NLR, respectively. According to the cut-off value of 7.35, high and low NLR was observed in 74 and 107 patients, respectively. The 30-day mortality was 37.8% in the high-NLR group versus 6.5% in the low-NLR group ($p < 0.001$). Multivariate logistic regression analysis after adjustment for potential confounders including age, IVH, ICH volume, GCS score, systolic and diastolic BP, confirmed the NLR > 7.35 as an independent predictor of 30-day death (OR 3.797, 95% CI 1.280–1.260).
Wang et al., 2018 [13]	Death occurred within 30 days from ICH onset in 40 (14.5%) patients. In patients who died, NLR was 2.4 (1.4–6.9) upon admission (T1), 11.3 (8.0–19.4) at 24–48 h (T2), and 12.9 (3.2–20.1) at 5–7 days (T3) ($p = 0.037$). In surviving patients, NLR values remained relatively stable: 3.3 (1.9–6.1) at T1, 4.9 (2.8–7.9) at T2, and 4.2 (2.5–6.3) at T3 ($p = 0.122$). At both T2 and T3, NLR was significantly higher in patients who died than in those who survived within 30 days ($p < 0.05$). In the multivariate analysis, the 30-day mortality was associated with both NLR_{T2} (OR 1.112, 95% CI 1.032–1.199; $p = 0.006$) and NLR_{T3} (OR 1.163, 95% CI 1.067–1.268; $p = 0.001$) after the adjustment for age, sex, ICH volume, GCS score, infra-tentorial ICH location, and presence of IVH.
Gökhan et al., 2013 [14]	A total of 868 patients with acute cerebrovascular events, including strokes and transient ischemic attacks, were included. Among the study cohort, 124 patients were diagnosed with hemorrhagic stroke. The mean hospital stay was 5.02 days (± 4.30) and in-hospital death occurred in 22 (17.7%) cases. The NLR values were significantly higher in dead than in surviving patients (10.80 ± 6.48 versus 3.78 ± 2.24; $p < 0.001$).
Lattanzi et al., 2018 [15]	One hundred and eleven (53.4%) patients had unfavorable 30-day outcome. The admission NLR values were 7.16 ± 5.10 and 2.95 ± 1.78 in patients with poor and good recovery, respectively ($p < 0.001$). At logistic regression, the NLR was significantly associated with 30-day functional status in the unadjusted (OR 1.69, 95% CI 1.42–1.95; $p < 0.001$) and adjusted (OR 1.49, 95% CI 1.24–1.79; $p < 0.001$) analysis after correction for potential confounders, including age, initial NIHSS score, baseline ICH volume, hematoma location, presence of IVH, and admission systolic BP. The addition of the NLR to the modified ICH score allowed to better classified patients according to 30-day status and improved the accuracy of outcome prediction by approximately 20%.
Giede-Jeppe et al., 2017 [16]	The median NLR on admission was 4.66 in the total cohort. Patients with above-average NLR values presented an increased risk of pneumonia, sepsis, need of ventilation, and external ventricular drain placement. Both mortality (178/427, 41.7% versus 127/428, 29.7%; $p < 0.001$] and unfavorable 3-month outcome (317/427, 74.2% versus 275/428, 64.3%; $p = 0.002$) were higher in patients with NLR ≥ 4.66. Admission NLR ≥ 4.66 was significantly associated with in-hospital mortality (OR 0.967, 95% CI 0.939–0.997; $p = 0.029$) and showed a trend on 3-month mortality (OR 0.974, 95% CI 0.945–1.004; $p = 0.087$). The thresholds of 2.606 and 8.508 were chosen as the 25th and 75th percentiles of admission NLR values. Patients with NLR < 2.606 had higher rates of favorable 3-month outcome (38.3 versus 28.9%; $p = 0.009$) and lower incidence of 3-month mortality (29.4 versus 38.1%; $p = 0.023$) compared to those with NLR ≥ 2.606). Both in-hospital mortality (28.5 versus 21.2%; $p = 0.041$), unfavorable 3-month outcome (80.8 versus 65.2%; $p < 0.001$), and 3-month mortality (44.4 versus 33.0%; $p = 0.002$) were significantly higher in patients with NLR ≥ 8.508.
Tao et al., 2017 [17]	At 3 months, 221 (65.8%) patients were classified as having poor outcome. They presented higher NLR compared to cases with favorable recovery [9.9 (5.6–16.6) versus 6.0 (3.7–11.7); $p < 0.001$]; death occurred in 90 (26.8%) patients, and their NLR values were more than twice those observed among surviving patients [13.6 (9.1–22.1) versus 6.4 (3.7–12.6); $p < 0.001$). At the ROC analysis, the NLR values of 6.28 (AUC 0.653) and 6.62 (AUC 0.767) were defined as the optimal thresholds to predict poor 3-month outcome and 90-day mortality, respectively. NLR > 6.28 was significantly associated with 3-month poor outcome (crude OR 3.6, 96% CI 2.3–5.8; $p < 0.001$; adjusted OR 2.6, 95% CI 1.4–4.7; $p = 0.002$). NLR > 6.62 was significantly associated with 90-day mortality (crude OR 6.4, 95% CI 3.3–15.5; $p < 0.001$; adjusted OR 5.1, 95% CI 2.6–8.6; $p < 0.001$). Multivariate analyses were adjusted for age, systolic blood pressure, GCS, ICH location, degree of midline shift, presence of subarachnoid hemorrhage, IVH, hematoma volume, and admission glucose.

Table 3 (continued)

Study	Main Findings
Lattanzi et al., 2016 [18]	Poor outcome patients (94/177, 53.1%) had higher NLR values compared to those with good functional status [6.88 (5.54) versus 3.25 (2.41); $p < 0.001$]. The NLR was associated with 3-month outcome in the logistic regression model before (OR 1.34, 95% CI 1.17–1.53; $p < 0.001$) and after (OR 1.16, 95% CI 1.02–1.33; $p = 0.031$) adjustment for the confounding effects of age, sex, initial and discharge NIHSS scores, baseline ICH volume, hematoma location, presence of IVH, admission systolic BP, and systolic BP variability. The optimal predictive cut-off threshold was set at 4.58, which yielded a 62.2% sensitivity and 84.9% specificity. At 3 months, 86.4 and 40.8% ($p < 0.001$) of the patients with NLR ≥ 4.58 and < 4.58 had a mRS score ≥ 3, respectively.
Sun et al., 2017 [19]	Patients were divided into quartiles according to admission NLR levels (Q1 < 2.78; Q2 2.78–4.08; Q3 4.08–7.85; Q4 ≥ 7.85). After 3-month follow-up, 148 (42.0%) participants experienced poor functional outcome and 47 (13.4%) died from all causes. Death or major disability was more common among patients in the highest compared to the lowest quartiles (60.23 versus 36.78%); in crude logistic model, admission NLR values ≥ 7.85 were associated with increased likelihood of unfavorable recovery (OR 2.60, 95% CI 1.41–4.79; $p = 0.008$).
Zhang et al., 2018 [20]	The rate of 3-month unfavorable outcome was 49.8% (112/225). The admission NLR values were markedly higher in patients presenting poor versus good 90-day prognosis [8.3 (6.9–12.1) versus 5.9 (3.7–7.4); $p < 0.01$]. The NLR was independently associated with 3-month functional status at logistic regression analysis before and after the adjustment for the effects of potential confounding variables, including history of ischemic stroke, time from onset to admission, duration of hospitalization, presence of subarachnoid hemorrhage, presence of IVH, GCS score, hematoma volume, and hydrocephalus (crude OR 1.07, 95% CI 1.02–1.16; $p < 0.01$; adjusted OR 1.82, 95% CI 1.24–2.62; $p < 0.01$). At the ROC analysis, the NLR value of 6.65 (AUC 0.694) was set as the optimal predictive threshold, yielding a sensitivity of 78.36% and a specificity of 63.72%.

AUC area under the curve, *BP* blood pressure, *CI* confidence interval, *ICH* intracerebral hemorrhage, *IVH* intraventricular hemorrhage, *mRS* modified Rankin Scale, *ND* neurological deterioration, *NIHSS* National Institutes of Health Stroke Scale, *NLR* neutrophil-to-lymphocyte ratio, *OR* odds ratio, *Q1-Q4* quartiles, *ROC* receiver operating characteristic

with reasonable accuracy. Moreover, survival may not represent the only meaningful endpoint and residual functionality may have even greater clinical and social relevance.

Currently available prognostic algorithms mostly take into account the major determinants of the primary injury, like hematoma volume, size and intra-ventricular extension [43] and cannot support highly accurate prediction of outcome. Indeed, there is accruing evidence that a multitude of metabolic, hemodynamic, and pharmacological factors can influence the stroke course [44–52], and a multidimensional assessment, which also include markers synthesizing the pathophysiological processes involved in secondary-induced damage, may better allow outcome prognostication.

The NLR outperformed the leukocyte counts as predictors of clinical outcome [10, 15, 18], improved the accuracy of prediction when added to the most common prognostic scale [15], and looks like a promising index to be included in clinical evaluation to refine the prognosis of patients with ICH.

Furthermore, the independent associations found across the studies between the NLR values and clinical endpoints after the adjustment for confounding variables, including the baseline neurological deficit, ICH volume, and location, play against the hypothesis that the NLR could only represent a surrogate marker of the ICH severity and physiologic acute stress reaction.

From the practical point of view, the NLR has the advantage to be an easily available and cost-effective index as readily estimated from laboratory parameters that are widely accessible and usually collected in routine medical practice. A standardized assessment of the NLR, however, is still lacking. All performed studies were mono-centric and characterized by relatively small sample size and heterogeneity in onset-to-sample times. Future efforts should be directed to determine the most appropriate schedule to obtain reproducible and valid estimates and identify the most predictive benchmark cut-off points according to baseline patient characteristics. The NLR is time-dependent, and values increase with time during the first few days following ICH. Moreover, it has been suggested that the critical thresholds may differ in relation to hematoma volume and clinical endpoint, with higher thresholds for larger than smaller ICHs and for mortality rather than poor functional status prediction [15, 17]. As a dynamic index, the additional informative value of the NLR trajectory over time to predict ICH prognosis should be further explored. Accordingly, prospective studies aimed to evaluate in parallel the time trends in cell counts and NLR values, cerebral edema and hematoma expansion, development of infections and post-stroke complications, and either short- or long-term outcomes are warranted to provide mechanistic insights into the underlying mechanisms. Since no therapy targeting ICH-induced primary injury has yielded conclusive benefits and ICH treatment remains mainly supportive within a framework of general critical care management, these findings would also contribute to identify new potential targets for neuro-protection and develop novel therapeutic strategies.

Compliance with Ethical Standards

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Ethical Approval This article does not contain any study with human participants performed by any of the authors.

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