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Prediction of the outcome of intracerebral hemorrhage by blood neutrophil to lymphocyte ratio: a prospective observational study

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Introduction: Intracerebral haemorrhage (ICH) is defined as bleeding within the brain parenchyma. Neutrophil lymphocyte ratio (NLR) is a dynamic parameter that can be affected by an underlying condition like microangiopathy (e.g. hemorrhagic stroke). The NLR value at the time of stress (e.g. ICH) could be a predictor among various other factors on the outcome of the disease. The aim of this study is to see if NLR could be a predictor of the outcome of the ICH.

Methods: This is a prospective observational study conducted in the Department of Neurosurgery and Department of Neurology, from March 2020 to February 2021. The ICH cases presented to the emergency department within 24 h of symptoms were included. The baseline haematological and biochemical investigations were sent and the noncontrast computed tomography (NCCT) head was done for the diagnosis of ICH. The NLR was measured. The ICH volume was calculated by ABC/2. Follow-up of the patient to measure outcome was done with a modified Rankin scale (mRS) on 30 days. Student's *t*-test was used to correlate NLR-mRS. Fischer's exact test was used for a categorical association of NLR to mRS.

Results: A total of 89 patients with ICH were enrolled in this study. In this study, 62.92% of patients had good outcomes (NLR of 4.88 ± 3.06), whereas 37.08% of patients had bad outcomes (NLR of 9.09 ± 4.92). Statistically, higher NLR was significantly predictive of poorer outcomes.

Conclusions: ICH causes stress in the body, which alters the value of NLR. Components of NLR are altered after haemorrhage due to a change in homeostasis of brain parenchyma. The NLR value obtained at the time of emergency department visits may help to predict the 30 days outcome of ICH.

Keywords: intracerebral hemorrhage, modified Rankin Scale, neutrophil lymphocyte ratio, NCCT

Introduction

ICH with or without intraventricular hemorrhage is a life-threatening subtype of stroke. It is the second common type among all strokes, which accounts for about 10–20%[1]. It has the worst outcome in terms of morbidity, disability, and mortality. Triaging of patients based on prognosis and customizing treatment is of utmost importance, especially in developing countries like Nepal to ensure optimal use of available limited resources. It has a fatality rate of around 40% in 1 month and 54% in 1 year[2].

Hypertension is the most important modifiable risk factor for spontaneous ICH. Deep perforator arteries in the thalamus, basal ganglia, midbrain, and deep cerebellar nuclei, are chronically damaged by hypertension. Other risk factors are trauma, cerebrovascular amyloid deposition, coagulopathies, thrombocytopenia, and cocaine use. Low levels of total serum cholesterol are

HIGHLIGHTS

- Intracerebral haemorrhage (ICH) is defined as bleeding within the brain parenchyma.
- ICH volume of a bleed can easily and rapidly be validated by the ABC/2 technique.
- Neutrophil-to-lymphocyte ratio (NLR), calculated as the ratio of neutrophil and lymphocyte cell counts in the peripheral blood.
- The NLR value obtained at the time of emergency department visits may help to predict the 30 days outcome of ICH.

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risk factors for ICH (in contrast to ischemic stroke, for which high cholesterol levels are a risk)[3].

Plain computed tomography (CT) head is the most rapidly available test for the diagnosis of ICH. The site of a bleed and calculation of the volume of a bleed can easily and rapidly be validated by the ABC/2 technique[4].

There are various prognostic factors. The most commonly used prognostic determinants include age of the patient, GCS at the time of admission, hematoma location and volume, and intraventricular extension, Essen ICH score, ICH score[5]. These scores, however, have some limitations and failed to support accurate prediction of outcome[6].

Neutrophil-to-lymphocyte ratio (NLR), calculated as the ratio of neutrophil and lymphocyte cell counts in the peripheral blood is fast emerging, easily available, low-cost, and reproducible prognostic indicator in several neurological disorders such as stroke, traumatic brain injury (TBI) and multiple sclerosis[6].

The host immune reaction following ICH initiates the inflammatory cascade attributed to interaction between and among immune-related cells-lymphocytes, and neutrophils. Following this variable inflammatory mediators, namely adhesion molecules (e.g. P-selectin), cytokines (e.g. IL-1, IL-6), chemokines (e.g. CCL2), and proteases (e.g. matrix metalloproteinase-9) are released.

The evidence have suggested that the inflammation contributes to tissue damage significantly caused by ICH. Specifically, activated inflammatory cells could release a variety of proinflammatory cytokines and proteases, which in turn cause secondary brain injury[7].

High neutrophils as innate immune cells enhance the neuroinflammatory cascade. It has a direct impact on brain edema and hematoma regrowth, increases mass effect and intracranial pressure, and results in neurological deterioration. Adaptive immune cells, and lymphocytes are crucial for the host's defense and adaptive immunity. Low lymphocyte count indicates a reduction of protective lymphocytes, which worsens outcomes by increasing the risk of infections in ICH patients.

NLR, thus, is a good marker that simultaneously shows susceptibility to secondary brain damage and poststroke complications secondary to neutrophil elevation and lymphocyte depletion[8]. Several studies have shown that the increased NLR is a negative prognostic indicator in acute ischemic stroke (AIS) and spontaneous intracerebral haemorrhage[9].

The aim of this study is to analyze the role of NLR in predicting outcomes in patients with acute ICH.

Methods

This is a prospective observational study conducted at the Department of Neurosurgery and the Department of Neurology from March 2020 to February 2021. In this study, patients presented to the emergency department (ED) within 24 h intracerebral hemorrhage were enrolled. Ethical clearance was obtained from the institutional review committee with reference number 333(6-11)^{E2} 076/077. The consent was taken from all the patients. The work has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) criteria[10].

All the patients above 18 years visiting to the ED with supratentorial ICH (diagnosed with a CT scan) and blood sample drawn within 24 h of the ED visit who were admitted under the Department of Neurosurgery and Department of Neurology were enrolled in the study. The patient with HIV/AIDS, hematological disorder, acute/chronic infection, autoimmune disease, cerebellar haemorrhage, and pontine haemorrhage, patients under steroid therapy and patient presented to ED after 24 h of symptoms were excluded from the study.

Considering the prevalence of 37% (similar study done in a medical college of Nepal) with a maximal permissible error of 10%, the sample size was calculated to be 89. (B) Sample size was calculated using the formula $n=z^2pq/d^2$.

Patients were stabilized at the beginning after arriving at the ED, and then, haematological, biochemical, and coagulation profiles were analyzed from a blood sample and an NCCT of the head were done. The site of bleed was noted and the volume of ICH was calculated by the 'ABC/2' formula. The haematological analysis, included total leucocyte count (TLC), neutrophil count, and lymphocyte count. The NLR value was calculated.

For blood pressure, the AHA/ASA guidelines were followed with a target BP of 160/90 mmHg by using intermittent or continuous intravenous medications. Patients with the feature of raised ICP were managed by elevating the head (30°), analgesics, and sedatives. Medical management was done with the mannitol (1.0–1.5 g/kg of 20% mannitol), hypertonic saline (3% NaCl), and neuromuscular paralysis. Hyperventilation was maintained for a rapid decrease in the ICP.

Immediate decompression craniectomy with/without hematoma evacuation and extraventricular drainage was placed for patients with neurological deterioration, brainstem compression, and/or hydrocephalus. Patients were admitted to the neurosurgery ward, neurology ward, surgical ICU, and central ICU on the basis of the patient's GCS, comorbidity, and vital status.

The length of hospital stay was taken at the time of discharge. For the patients already discharged, phone calls were made on the 30th day of the onset of symptoms. The patient's physical condition was inquired with family members/caretakers. The patient's condition was noted and graded as per the modified Rankin Scale.

Data were analyzed using SPSS 25. Continuous variables were expressed as means ± SD. Quantitative data were analyzed by *t*-test. Continuous variables were analyzed by Fischer's exact test. The statistical significance of the test was set at $P < 0.05$.

Results

In this prospective observational study, a total of 107 patient's data were taken. Eighteen (16.8%) patients were excluded; eight (44.44%) cases visited the hospital after 24 h of symptoms, six (33.33%) cases had cerebellar haemorrhage, two (11.11%) patients could not be followed as their phone number was not recorded correctly, two (11.11%) cases had incomplete investigations, and a total of 89 (83.17%) patients were included in the data analysis.

Correlation between NLR and Modified Rankin Scale

Among the study group, 56 (62.92%) patients had a good outcome, with a mean NLR value of 4.88 ± 3.06 and 33 (37.08%) patients had a bad outcome with an NLR value of 9.09 ± 4.92. The NLR value is significantly associated with mRS (30 days outcomes of ICH) with a *P*-value of < 0.001 [95% CI: –5.90 to –2.53] as shown in Table 1.

Table 1

mRS-NLR correlation

mRS	NLR Mean ± SD	P	95% CI
Good out come (0–2) $N = 56$	4.88 ± 3.06	< 0.001*	−5.90 to −2.53
Bad out come (≥ 3) $N = 33$	9.09 ± 4.92		

mRS, modified rankin scale.

Categorical analysis of NLR with mRS

The descriptive statistics of mRS across all five categories of NLR are reported in Table 2. On categorical analysis, the bad outcome group had a high NLR value. Similarly, the good outcome group had a low NLR value. mRS was positively correlated with the categorical subgroup of NLR with a *P*-value of < 0.001 as shown in Table 2.

Correlation between NLR and volume of ICH

In our study, NLR and volume of ICH are moderately correlated with NLR value, which is strongly supported by a significant *P*-value ($P < 0.05$) as shown in Table 3.

Demography and other characteristic

Among the total 107 patients, there were 77 (71%) males and 30 (29%) females. The most common age group in this study was 60–69 years of age. The mean age (mean ± SD) was of 60.78 ± 15.05 years with ages ranging from 23 to 88 years of age.

In this study, 63 patients were hypertensive, with a mean systolic blood presssure of 169.49 ± 34.26. Six patients had a history of trauma, and four cases presented after rupture of the aneurysm. Fourteen patients (12 males and 2 females) had other causes (unspecified). These patients had normal SBP and a mean age of 57.7 ± 15.9 year as shown in Figure 1.

Among all the patients who presented to our center, 67.41% patient had thalamic bleed (basal ganglia), 17.9% had parietal bleed, 5.61% had fronto-parietal bleed, 4.49% had frontal bleed, 2.24% had occipital bleed and 1.12% had frontal bleed and 1.12% parieto-occipital bleed as shown in Figure 2.

Discussion

ICH is common in old age. Hypertension is the most common cause of ICH. Previous studies results are closely related to the NLR as a prognosis of STROKE[11]. In patients with a positively, high NLR value is associated with 30-day mortality (Wang *et al.* 2016) as well as 90-day mortality (Lattanzi *et al.* 2016a, b; Tao *et al.* 2017)[12,13]. In our study, among 89 cases of ICH, 33 (37.07%) cases had modified Rankin Scale of ≥ 3 (i.e. bad outcome) at 1 month. The association between the NLR value at the time of the ED visit and the outcome of ICH at 30 days follow up was statistically significant ($P < 0.001$). In the study done by Fie Wang *et al.*[14] with 181 cases, 74 had a high NLR value (> 7.35); 107 had a low NLR value (≤ 7.35). The 30-day mortality was 37.8% (28/74) in the high-NLR group vs. 6.5% (7/107) in the low-NLR group ($P < 0.001$). In our study, on categorical analysis, the NLR value category is statistically significant with mRS ($P < 0.001$). However, no other studies have analyzed categorical analysis of NLR value.

During haemorrhage in the brain parenchyma, neutrophils are the earliest WBCs to appear in clots and peaks in a few days[15,16]. Neutrophil releases a large number of cytokines, including TNF alpha. According to Behrouz *et al.* 2016, the concentration of TNF in the blood is directly proportional to ICH volume[17]. Neutrophils could disrupt the BBB and neurons by releasing reactive oxygen species (ROS), and proinflammatory cytokines, upregulating the expression of metalloproteinase[18]. Neutrophils also stimulate microglia/macrophages to release a variety of cytokines and free radicals[16].

Lymphocyte acts as adaptive immunity to potentiate brain injury. In a study done by Rolland WB *et al.*[19] 2013, a drug that reduces the T cell pool reduces cerebral edema by regulating IL-17.

NLR is an independent predictor of 30 days mortality of ICH, however, many other factors like hematoma regrowth, blood pressure variability, and other inflammatory markers interleukin, TNF-α does have a significant role in the ICH outcome[14].

In a study done by Fei Wang *et al.*, ICH patients with low NLR (≤ 7.35) had a mean ICH volume of 6 cm^3 and patients with high NLR (> 7.35) had a mean ICH volume of 23.9 cm^3 ($P < 0.001$)[19]. Similarly to other studies, the association of NLR value and ICH volume was statistically significant in our study. The volume of bleed acts as the physical destructor of the neurons. In addition to the mass effect, the peri hematoma edema also contributes to progressive tissue injury and poor neurological outcomes after ICH[20]. In patients with ICH, low leucocyte

Table 2

Categorical NLR-mRS correlation

mRS	NLR 1–3	3–5	5–9	9–18	> 18	Row total (*N*)	P
Good outcome (0–2)	16	17	19	3	1	56	< 0.001*
Bad outcome (≥ 3)	4	3	7	17	2	33	
Column total (*n*)	20	20	26	20	3	89	

mRS, modified rankin scale.

Table 3

Correlation between volume of ICH and NLR

Variables	Mean ± SD	Pearson correlation (r)	P
Volume of bleed (ml)	26.40 ± 23.5	0.425	< 0.001*
NLR	6.44 ± 4.35		

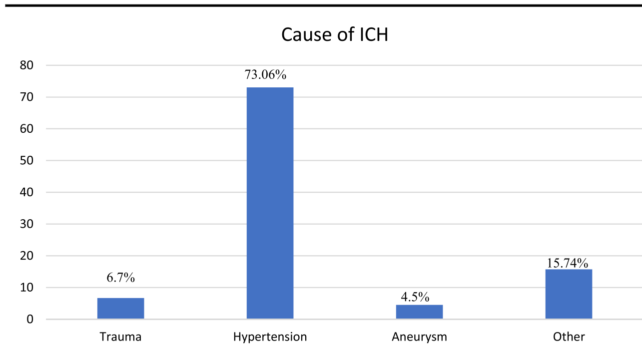

Figure 1. Cause of intracerebral haemorrhage.

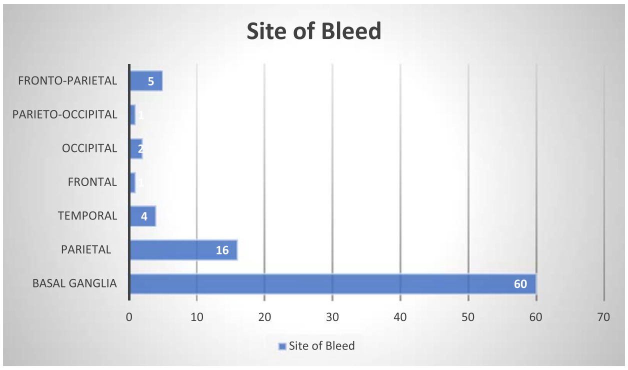

Figure 2. Site of bleeding.

count is associated with 90-day mortality and poor neurological recovery[21,22]. In this study, lower lymphocyte count with high mRS is consistent with these previous studies.

In a study done by, Nilsson[23] the common age group of ICH was found to be 74–84 years. Similarly, a study done by Hegde *et al.*[24], showed the mean age of ICH patients was 58.10 ± 12.76, which is similar to our study with a mean age of 60.78 ± 15.05. In this prospective observational study, the most common age group of ICH patients belongs to 60–69 years, which accounts for 26.96%.

Our study had several limitations. Firstly, this is a single-center observational study. Second, the sample size is small. Third, we did not enroll proinflammatory markers in this study. Fourth, we did not record changes in blood pressure as its variability has a strong association with poor outcomes in ICH[25]. Fifth, in this study, we did not validate the biochemical parameters which has strong associations with outcomes of the ICH[26].

Conclusions

We conclude that the NLR value at the time of presentation at the emergency department (within 24 h of symptoms) can predict the outcome of ICH at 30 days. There is a moderate association between NLR value and ICH volume.

Ethical approval

Ethical clearance was obtained from institutional review committee, Institute of Medicine, Kathmandu, Nepal. Reference number 333(6-11)^{E2} 076/077.

Consent

Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

G.S., A.G., R.V., A.H., and A.S.K.: were involved in study design, data collection, analysis and interpretation, and writing manuscript; A.S., B.D., A.N., R.A., and A.S.: were involved in data analysis and manuscript revision; G.S.: was involved in data analysis and final manuscript editing. All authors approved the final submission

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Guarantor

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Data availability statement

Will be available on request from the concerned authority.

Provenance and peer review

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References

[1] Sacco S, Marini C, Toni D, *et al.* Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. Stroke 2009;40:394–9.
[2] An SJ, Kim TJ, Yoon BW. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update. Journal of Stroke Korean Stroke Society 2017;19:3–10.
[3] Lattanzi S, Cagnetti C, Provinciali L, *et al.* Neutrophil-to-lymphocyte ratio and neurological deterioration following acute cerebral hemorrhage. Oncotarget 2017;8:57489–94.
[4] de Oliveira Manoel AL, Goffi A, Zampieri FG, *et al.* The critical care management of spontaneous intracranial hemorrhage: a contemporary review. Crit Care 2016;20.
[5] Portenoy RK, Lipton RB, Berger AR, *et al.* Intracerebral haemorrhage: a model for the prediction of outcome. Neurosurgery, and Psychiatry 1987;50:976–9.
[6] Menon G, Johnson SE, Hegde A, *et al.* Neutrophil to lymphocyte ratio – a novel prognostic marker following spontaneous intracerebral haemorrhage. Clin Neurol Neurosurg 2021;200:106339.
[7] Zhao X, Sun G, Zhang J, *et al.* Hematoma resolution as a target for intracerebral hemorrhage treatment: role for peroxisome proliferator-activated receptor γ in microglia/macrophages. Ann Neurol 2007;61:352–62.
[8] Patient characteristics (n = 868).
[9] Song SY, Zhao XX, Rajah G, *et al.* Clinical significance of baseline neutrophil-to-lymphocyte ratio in patients with ischemic stroke or hemorrhagic stroke: an updated meta-analysis. Vol. 10Frontiers in Neurology. Frontiers Media S.A; 2019.
[10] Mathew G, Agha R. for the STROCSS Group. STROCSS 2021: strengthening the reporting of cohort, cross-sectional and case-control studies in surgery. Int J Surg 2021;96:106165.
[11] Aktimur R, Cetinkunar S, Yildirim K, *et al.* Neutrophil-to-lymphocyte ratio as a diagnostic biomarker for the diagnosis of acute mesenteric

ischemia. European Journal of Trauma and Emergency Surgery 2016;42: 363–8.
[12] Wang F, Hu S, Ding Y, *et al*. Neutrophil-to-lymphocyte ratio and 30-day mortality in patients with acute intracerebral hemorrhage. Journal of Stroke and Cerebrovascular Diseases 2016;25: 182–7.
[13] Lattanzi S, Cagnetti C, Provinciali L, *et al*. Neutrophil-to-lymphocyte ratio predicts the outcome of acute intracerebral hemorrhage. Stroke 2016;47:1654–7.
[14] Wang F, Wang L, Jiang T ting, *et al*. Neutrophil-to-lymphocyte ratio is an independent predictor of 30-day mortality of intracerebral hemorrhage patients: a validation cohort study. Neurotox Res 2018; 34:347–52.
[15] Wang J. Preclinical and clinical research on inflammation after intracerebral hemorrhage. Progress in Neurobiology 2010;92: 463–77.
[16] Wang J, Doré S. Inflammation after intracerebral hemorrhage. Journal of Cerebral Blood Flow and Metabolism 2007;27:894–908.
[17] Behrouz R. Re-exploring tumor necrosis factor alpha as a target for therapy in intracerebral hemorrhage. Transl Stroke Res 2016;7: 93–6.
[18] Moxon-Emre I, Schlichter LC. Neutrophil Depletion Reduces Blood-Brain Barrier Breakdown, Axon Injury, and Inflammation After Intracerebral Hemorrhage [Internet]. 2011. http://jnen.oxfordjournals.org/
[19] Rolland WB, Lekic T, Krafft PR, *et al*. Fingolimod reduces cerebral lymphocyte infiltration in experimental models of rodent intracerebral hemorrhage. Exp Neurol 2013;241(1)):45–55.
[20] Murthy SB, Moradiya Y, Dawson J, *et al*. Perihematomal edema and functional outcomes in intracerebral hemorrhage: influence of hematoma volume and location. Stroke 2015;46:3088–92.
[21] Morotti A, Marini S, Jessel MJ, *et al*. Lymphopenia, infectious complications, and outcome in spontaneous intracerebral hemorrhage. Neurocrit Care 2017;26:160–6.
[22] Giede-Jeppe A, Bobinger T, Gerner ST, *et al*. Lymphocytopenia is an independent predictor of unfavorable functional outcome in spontaneous intracerebral hemorrhage. Stroke 2016;47:1239–46.
[23] Nilsson OG. Incidence of intracerebral and subarachnoid haemorrhage in southern Sweden. J Neurol Neurosurg Psychiatry 2000;69:601–7; Available from www.jnnp.com
[24] Hegde A, Menon G, Kumar V, *et al*. Clinical profile and predictors of outcome in spontaneous intracerebral hemorrhage from a tertiary care centre in south india. Stroke Res Treat 2020;2020:1–8.
[25] Lattanzi S, Silvestrini M. Blood pressure in acute intra-cerebral hemorrhage. Ann Transl Med 2016;4:320.
[26] Anuska Roy. Assessment of prognosis of intracerebral haemorrhage with respect to clinical, biochemical and radiological parameters: a study in a tertiary health care centre in Eastern India. Medical Research Journal 2023;8:179–85.