The prognostic value of neutrophil-to-lymphocyte ratio in patients with traumatic brain injury: A systematic review

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Traumatic brain injury (TBI) places a heavy load on healthcare systems worldwide. Despite significant advancements in care, the TBI-related mortality is 30–50% and in most cases involves adolescents or young adults. Previous literature has suggested that neutrophil-to-lymphocyte ratio (NLR) may serve as a sensitive biomarker in predicting clinical outcomes following TBI. With conclusive evidence in this regard lacking, this study aimed to systematically review all original studies reporting the effectiveness of NLR as a predictor of TBI outcomes. A systematic search of eight databases was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement (PRISMA) recommendations. The risk of bias was assessed using the Quality in Prognostic Studies (QUIPS) tool. Eight studies were ultimately included in the study. In most of the studies interrogated, severity outcomes were successfully predicted by NLR in both univariate and multivariate prediction models, in different follow-up durations up to 6 months. A high NLR at 24 and 48 h after TBI in pediatric patients was associated with worse clinical outcomes. On pooling the NLR values within studies assessing its association with the outcome severity (favorable or not), patients with favorable outcomes had 37% lower NLR values than those with...
Introduction

As one of the leading causes of death worldwide, traumatic brain injury (TBI) places a heavy burden on healthcare systems worldwide despite significant advancements in care (1). A recently published epidemiological study suggested that the age-adjusted mortality rate of TBI was 13–17 per 100,000 subjects (2). Furthermore, many reports have shown that the frequency of TBI mortality is 30–50% and that most cases involve adolescents or young adults (3–5). An additional socioeconomic burden on patients’ families and community is a frequent consequence of major disabilities among survivors of TBI (1).

While primary brain damage is irreparable, secondary brain injury due to trauma-induced oxidative stress, ischemia, edema, and systemic response to inflammation can be remedied (1, 6–11). The inflammatory response following TBI is not fully understood, yet recent literature has demonstrated that such an inflammatory response might be prompted by damaged neuronal tissue. This damage triggers the production of proinflammatory cytokines and several angiogenic factors (12). This process further progresses to degeneration of tight junctions and protein extravasation (13). The uncontrolled release of inflammatory mediators, as well as the improper activation of endothelial cells, can affect the integrity of the blood-brain barrier (BBB), leading to fluid leakage to the interstitium and marked leukocytic infiltration (14). An in vitro study revealed that alteration of the BBB after the neuronal inflammatory response facilitates the migration of neutrophils into the injured area within the first hour of brain trauma, which may further affect the circulating white blood cells (WBCs) (15).

Assessment of peripheral WBCs, in terms of total and differential cell counts, is a straightforward and inexpensive test that provides a broad view of the entire systemic inflammatory process. Elevated WBC count was observed after delayed cerebral ischemia and deemed an independent risk factor for cerebral vasospasm after subarachnoid bleeding (16). Furthermore, the neutrophil-to-lymphocyte ratio (NLR) was proposed as a sensitive predictor of the inflammatory response in various neurological and non-neurological diseases such as stroke, Alzheimer’s disease, and cardiovascular disorders (17–19). Moreover, it has been associated with poor clinical outcomes in certain types of cancer (20, 21). Similarly, reports have demonstrated that the NLR may serve as a sensitive biomarker in predicting clinical outcomes following TBI. Although conclusive evidence in this regard is lacking, these findings warrant further larger studies (22, 23). Therefore, this study aimed to systematically review all original studies reporting the effectiveness of NLR as a predictor of TBI outcomes.

Methods

Search strategy and study selection

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Review and Meta-Analyses statement (PRISMA) recommendations (24) using the AutoLit platform (Nested Knowledge, St. Paul, MN). We formulated the PICO question according to the following: population: patients with TBI; intervention: the neutrophil/lymphocyte sampling; comparator: healthy individuals/controls whenever available; outcome: the prognostic value of the NLR (e.g., mortality, morbidity, or improvement). After collecting the appropriate keywords for developing a search term (neutrophil* OR lymphocyte*) AND ratio* AND (Brain Injuries, Traumatic[MeSH] OR Trauma[Title]), we performed a systematic search for collecting relevant studies followed by a manual search from references to avoid missing any relevant papers. For databases not supporting MeSH terms, we used a combination of all possible keywords. The search was conducted on January 30, 2021, in eight databases: PubMed, Google Scholar, Embase, Scopus, Web of Science, The New York Academy of Medicine (NYAM), Virtual Health Library (VHL), and the System for Information on Grey Literature in Europe (SIGLE).
We included original studies that investigated the prognostic value of the NLR in patients with TBI. We excluded studies if they were (1) animal studies, (2) non-English articles, (3) non-original investigations such as protocols, reviews, posters, abstracts, and (4) case reports and case series of <5 patients. Title and abstract screening and full-text screening were done by at least two reviewers. The senior author was responsible for solving conflicts between the two reviewers.

Data extraction

We conducted a pilot extraction of a few included studies for constructing a data extraction sheet. Then, two reviewers retrieved the necessary data from each of the included papers. The extraction sheet included the study design of the included papers, reference ID, demographic of the included population, outcomes of interest, and risk of bias tool. The senior author was responsible for solving conflicts between the two extractors.

Risk of bias

Three independent reviewers evaluated the risk of bias in included studies. The risk of bias was assessed using the Quality in Prognostic Studies (QUIPS) tool (25, 26). Any discrepancy between the reviewers was solved by discussion.

Statistical analysis

All data were analyzed using R software version 4.2.1. and the "meta" package. We did a priori sensitivity analysis comparing Standardized Mean Difference and Ratio of Means (RoM) computed results; in the case of similar results, RoM and its 95% confidence intervals (CI) were adopted due to easier interpretation of the results (27, 28). The analysis was conducted using a random-effects model due to considerable heterogeneity among the included studies. Heterogeneity was assessed with Q statistics and I² test considering it significant with I² value >50% or P-value <0.05 (29, 30). Due to the small number of the included studies (<10 per the analysis), neither Egger's regression test for assessing publication bias nor meta-regression was possible (31).

Results

Search results

Following the combination of search results from all databases, a total of 1,568 records were retrieved. After removing duplicates using EndNote software (Clarivate Analytics, Philadelphia, PA), 1318 unique records were retained. The title and abstract screening filtered irrelevant papers to 29 records, which were further filtered by the full-text screening to seven relevant papers. We found one relevant paper using manual search methods to include a total of eight papers in the current study (Figure 1).

Characteristics of the included studies

Details of the studies included in this systematic review are available in Table 1. Participants were included from several countries, including the United States (US), Turkey, China, Poland, and Australia. Of the eight included studies, seven were retrospective, and one employed a prospective study design. The timeframe of these studies was from January 1st, 2004, through December 31, 2017. The sample sizes ranged from 144 to 1291 patients. The seven retrospective studies used several severity measurements and scores. All retrospective studies used the Glasgow Coma Scale (GCS). Other metrics including Glasgow Outcome Scale-Extended Pediatric Version (GOS-E Peds), level of consciousness, post-traumatic amnesia, and Extended Glasgow Outcome Scale (GOSE). The prospective study by Akilli et al. (32) used the GCS, Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE-II), and Sequential Organ Failure Assessment (SOFA) severity measurements. Generally, all included studies investigated the prognostic role of NLR. The retrospective study by Corbett et al. (33), which was based in Australia, specifically included patients who underwent decompressive craniectomy following severe TBI. Moreover, the retrospective study by Kimball et al. (22) based in the US specifically included patients aged 0 to 18. Three of the included studies (32, 34, 35) excluded patients with ages <18 and a history of hepatic or hematologic disease. Additionally, two of the eight studies (32, 35) screened out pregnant patients. Furthermore, we excluded studies that appeared as online only.

Characteristics of the included patients

Details of patient characteristics are in Table 1. The US retrospective study (15) had a mean patient age of 9.49 (SD: 6.70) years with a median length of stay of 3 (range: 1–48) days. The other five retrospective studies had mean ages ranging from 45.40 (14.85) to 47.03 (16.88) years and median ages ranging from 33 to 56 years. The Australia-based study had a median length of stay of 23 (IQR: 13–45) days (21). The prospective study by Akilli et al. (32) had a median patient age of 74 years with a median length of stay of 6.0 (IQR: 9.1) days. The gender distribution of the retrospective studies ranged from 63 to 92% male, with the prospective study having 54.4% male patients. Only two studies included survival data, which were 96% for the US study (15) in 2020 and 64% for
Chen et al. (34) in 2018. The one prospective study had a median patient GCS score of 12 on admission (8). Chen et al. (34) conducted a retrospective study that included patients’ clinical characteristics, including means of 130.54 (SD: 25.50) mmHg for systolic arterial pressure, 76.85 (SD: 15.53) mmHg for mean arterial pressure, 95.12 (SD: 17.93) mmHg for diastolic arterial pressure, 85.7 (SD: 25.2) beats/min for heart rate, 36.86 (SD: 0.68) °C for body temperature, 95.35% (SD: 4.37%) blood oxygen saturation, 9.75 (SD: 3.41) mmol/L for blood glucose, and 5.95 (SD: 1.69) GCS score on admission. The 2019 retrospective study by Chen et al. (23) demonstrated clinical characteristics, including medians of 136 (IQR: 123–150) mmHg for systolic arterial pressure, 79 (IQR: 70–88) mmHg for diastolic arterial pressure, 89.5 (IQR: 79–109) beats/min for heart rate, 36.8 (IQR: 36.6–37.2) °C for body temperature, 8.7 (IQR: 7.4–10.38) mmol/L for blood glucose, and 7 (IQR: 5–8) for GCS score on admission.

Quality assessment of the included studies

QUIPS quality scores for risk of bias are presented in Table 2. Overall, the methodological quality of the included studies was satisfactory. Study participation and attrition were rated at a high risk of bias in one of the studies (34). All of the studies had a low to moderate risk of bias for prognostic factor measurement and outcome measurement. Furthermore, all of the studies were deemed acceptable with minimal risk of bias on statistical analysis and reporting.

NLR value and prognosis

Relevant data of NLR values, outcome(s), outcome scale(s), and multivariate prediction model results (when applicable) are
TABLE 1  Study and baseline characteristics of included studies and participants.

| Study and baseline characteristics | Kimball et al. (22) | Acar et al. (47) | Akilli et al. (32) | Chen et al. (34) | Zhao et al. (36) | Chen et al. (23) | Siwicka-Gieroba et al. (35) | Corbett et al. (33) |
|-----------------------------------|---------------------|-----------------|-------------------|-----------------|----------------|-----------------|--------------------------|-----------------|
| **Study characteristics**         | USA                 | Turkey          | Turkey            | China           | China          | China           | Poland                   | Australia |
| Country                           | Retrospective       | Retrospective   | Prospective       | Retrospective   | Retrospective  | Retrospective   | Retrospective            |                  |
| Study design                      | January 01, 2007    | January 01, 2013| January 01, 2013  | December 2004   | December 2017  | December 2017  | Retrospective NR       | Retrospective    |
| Time frame                        | December 31, 2017   | December 31, 2014| August 10, 2013   | April 2012      | January 2017   | January 2017   | Retrospective           | Retrospective 2004 - 2016 |
| Sample size                       | N = 188             | N = 373         | N = 688           | N = 1291        | N = 316        | N = 144         | N = 388                  |                  |
| Inclusion criteria                | Age 0–18 years, isolated TBI, and at least one CBC panel with differential taken within 84 h of the time of injury | Patients with minor head trauma with isolated head trauma | Patients who had 2 of the 4 systemic inflammatory response syndrome criteria | CT scan confirmed patients with TBI, CT signs of TBI, patients had to be > 14 years of age, Patients had to be admitted within 6 h after injury | Patients with TBI with traumatic injury to a body region other than the brain with an Abbreviated Injury Severity score > 3 and those with (34) penetrating brain injury | Patients aged < 18 years, pregnant women, patients with drug overdoses, patients with a history of neoplastic, cardiac, hepatic diseases, or renal diseases. |                  |                  |
| Exclusion criteria                | Severe comorbidities, prior neurological disease, anticoagulant, steroids, or immunosuppressants use, and prior systemic disease | Patients with GCS scores below 15, multiple traumas, chest pain, anemia, or chronic renal failure | Age <18 years, pregnancy, hematologic disease, previous chemotherapy, blood transfusion, chronic hepatic disease, trauma, or poisoning. | Age <18 years, time from injury to admission > 6 h, previous head trauma, ischemic or hemorrhagic stroke, antithrombotic, anticoagulants, steroids, immunosuppressants use presence of prior systemic diseases | History of head trauma or other major diseases such as stroke, tumor, uremia, and heart failure. Missing data or loss to follow-up. | None |                  |
| Severity measurement/scores       | GOS-E Peds, LOC, GCS, PTA | CT scan findings | GCS, APACHE II, SOFA | GOS, GCS | GCS, GOS | GCS, GOS | GCS, GOSE | GOS, GCS |
| Baseline characteristics of included participants | Age, years | 9.49 ± 6.70a | 35.25 ± 20.25a | 74 (19)b | 45.40 ± 14.85a | 47.03 ± 16.88a | 56 (43–63)b | 48 (32–59)b |

(Continued)
| Study and baseline characteristics | Kimball et al. (22) | Acar et al. (47) | Akilli et al. (32) | Chen et al. (34) | Zhao et al. (36) | Chen et al. (23) | Siwicka-Gieroba et al. (35) | Corbett et al. (33) |
|----------------------------------|--------------------|-----------------|-------------------|-----------------|-----------------|-----------------|--------------------------|----------------|
| Length of Hospital Admission, days | 3, (1–48)b | NR | 6.0 (9.1)b | NR | NR | 18 (12–25.75) | NR | 23 (13–45)b |
| Gender | | | | | | | | |
| Male | 118 (63 %) | 151 (75.5 %) | 203 (54.4 %) | 557 (81 %) | 982 (76.1 %) | 256 (81.0 %) | 118 (92 %) | 310 (80 %) |
| Type of injury | | | | | | | | |
| Skull fracture | NR | 28 (14%) | NR | NR | 299 (23.2 %) | NR | NR | NR |
| Diffusion axonal injury | NR | NR | NR | NR | 46 (3.6 %) | NR | NR | NR |
| Epidural hematoma | NR | 27 (14%) | NR | NR | 368 (28.5 %) | NR | NR | 24 (6 %) |
| Subdural hematoma | NR | 24 (12%) | NR | NR | 378 (29.3 %) | NR | NR | NR |
| Subarachnoid hemorrhage | NR | 15 (08%) | NR | NR | 649 (50.3 %) | NR | NR | 361 (93 %) |
| Intracerebral hematoma | NR | 06 (03%) | NR | NR | 860 (66.6 %) | NR | 19 (13.2 %) | NR |
| Clinical characteristics | | | | | | | | |
| Systolic arterial pressure, mm Hg | NR | NR | NR | 130.54 ± 25.50a | NR | 136 (123–150)b | NR | NR |
| Diastolic arterial pressure, mm Hg | NR | NR | NR | 76.85 ± 15.53a | NR | 79 (70–88)b | NR | NR |
| Mean arterial pressure, mm Hg | NR | NR | NR | 95.12 ± 17.93a | NR | NR | NR | NR |
| Heart rate, beats/min | NR | NR | NR | 85.7 ± 25.2a | NR | 89.5 (79–109)b | NR | NR |
| Body temperature, °C | NR | NR | NR | 36.86 ± 0.68a | NR | 36.8 (36.6–37.2)b | NR | NR |
| Blood oxygen saturation, % | NR | NR | NR | 95.35 ± 4.37a | NR | NR | NR | NR |
| Blood glucose level, mmol/L | NR | NR | NR | 9.75 ± 3.41a | NR | 8.7 (7.4–10.38)b | NR | NR |
| GCS Score on Admission | NR | NR | 12 (8)b | 5.95 ± 1.69a | 11.21 ± 3.70a | 7 (5–8)b | 5 (3–6)b | 8 (5–11)b |
| Survival | 181 (96 %) | 184 (92 %)* | NR | 440 (64 %) | NR | NR | NR | NR |

TBI, Traumatic brain injury; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; GOS-E Peds, Glasgow Outcome Scale-Extended Pediatric; APACHE II, Acute Physiology And Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment score; LOC, Loss of consciousness; PTA, Post Traumatic Amnesia; NA, Not applicable; NR, Not reported; a, Mean ± SD; b, Median (IQR); *number of dead is unknown.
The statistical analysis is appropriate for the design of the study? Important potential confounders are accounted for? The outcome of interest is adequately measured in study subjects? Does the study sample provide outcome data adequate? The study sample represents the population of interest on key characteristics? The study confounding 6. Statistical analysis 7. Outcome measurement 8. Prognostic factor measurement

| Study | 1. Study participation | 2. Study attrition | 3. Prognostic factor measurement | 4. Outcome measurement | 5. Study confounding | 6. Statistical analysis | 7. Outcome measurement | 8. Prognostic factor measurement |
|-------|-----------------------|-------------------|-----------------------------|-----------------------|---------------------|----------------------|-----------------------|-----------------------------|
| Kimball et al. (22) | Yes | Partly | Fail | No | Not clear | Not clear | Yes | Yes | No |
| Corbett et al. (33) | Partly | Partly | Fail | No | Not clear | Not clear | Yes | Yes | Yes |
| Zhao et al. (34) | No | Fail | Partially | Yes | Yes | Yes | Yes | Yes | Yes |
| Chen et al. (35) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Acar et al. (36) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Siwicka-Gieroba et al. (37) | Yes | Partially | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

Studies were assessed under six domains of the QUIPS tool and given a rating (yes, no, partly, unclear; Hayden et al. (20)). A “yes” response indicates that the study has been designed and conducted to sufficiently limit the potential bias in that domain. An “unclear” or “partly” response arises when the answer to an item is not reported or is not reported clearly.

Discussion

TBI affects millions of individuals worldwide on a yearly basis (37). This creates a taxing burden on healthcare systems in terms of financial resources or associated mortality. The pathophysiology of TBI is a highly complex process that relies on the primary brain injury resulting from the external injury (38) and the secondary injury that takes place within minutes of the primary one and can continue for several days.
### TABLE 3  NLR value and prediction according to worse outcomes.

| Source timeline | Outcome | Outcome score | NLR value | Multivariate prediction model of outcome |
|-----------------|---------|---------------|-----------|-----------------------------------------|
|                 |         |               | Favorable/ alive* | Unfavorable/ dead* | Significance | Variables included |
|                 |         |               | GOS-E 1 - 2 | GOS-E 3 - 6 | GOS-E 7 - 8 | P = 0.38 | NR | NR | NR | NR |
| < 12 h Severity | GOS-E Peds | 4.15 ± 5.87a | 6.79 ± 8.42a | 4.13 ± 4.94a | P = 0.004 | NR | NR | NR | NR |
| 24 h Severity   | GOS-E Peds | 4.25 ± 3.43a | 7.84 ± 4.27a | 9.08 ± 4.55a | P = 0.003 | NR | NR | NR | NR |
| 48 h Severity   | GOS-E Peds | 4.92 ± 3.05a | 5.86 ± 2.98a | 11.22 ± 1.95a | P = 0.80 | OR (95 % CI) 1.003 (0.972–1.035) | IMPACT predicted risk; Hemoglobin, g/dL; Total white blood cells, ×109/L; NLR; Platelets, ×109/L; Fibrinogen, g/L; INR; aPTT, sec; DIC score; Glucose, mmol/L |
| 72 h Severity   | GOS-E Peds | 7.96 ± 12.50a | 6.45 ± 3.58a | 11.45 ± 2.85a | P = 0.996 | NR | NR | NR | NR |
| 18 month Severity | GOS | 6 (2–12)b | NA | 6 (3–11)b | P < 0.05 | Adj OR (95 % CI) 0.91 (0.89 - 0.93) | P = 0.001 | White blood cells, ×109/L; Neutrophil ratio; Lymphocyte ratio; NLR |
| 28 day Mortality | NA | NA | NA | NA | P < 0.05 | NR | NR | NR | NR |
| 6 month Severity | GOS | 07.68 ± 06.54a | 24.71 ± 12.52a | P < 0.001 | OR (95 % CI) 1.197 (1.125–1.273) | P < 0.001 | Day 1 NLR; Admission GCS score |
| 12 day (NLR peak) Severity | GOS | 11.55 (08.62–14.11)b | 17.62 (13.08–20.89)b | P < 0.001 | OR (95 % CI) 1.197 (1.125–1.273) | P < 0.001 | Day 1 NLR; Admission GCS score |
| 1 Year Mortality | NA | 13.75 ± 6.27a | 18.75 ± 7.76a | P < 0.001 | Model I: OR (95 % CI) 1.141 (1.085–1.200) | P < 0.001 | NLR; Deterioration; Mechanical ventilation |
|                  |         |               |           |               | Model II: OR (95 % CI) 1.158 (1.094–1.226) | P < 0.001 | Temperature, ∘C; NLR; Deterioration; Mechanical ventilation |

(Continued)
null
Comparison of neutrophil-lymphocyte ratio (NLR) in patients with favorable outcomes to those with unfavorable ones.

upon admission and the presence of post-traumatic amnesia failed to show any significance in predicting clinical outcomes. Higher values of the NLR at 24 and 48 hours were associated with less favorable outcomes in pediatric patients suffering from TBI. Furthermore, patients who lost consciousness also had a significantly elevated NLR compared with patients who maintained consciousness (22).

In patients with minor head trauma, a retrospective study of 200 patients used computerized tomography (CT) scanning and blood markers to assess brain dysfunction in patients whose GCS were graded as 15 (47). Patients with normal CT scans served as the controls in this study. Blood values that were clinically significant included NLR and troponin-T. The NLR had a specificity of 90% when a cutoff value of 4.29 was implemented in assessing patients with detectable brain pathology on head CT in comparison with those who did not (47). This suggests that the NLR may have utility in patient assessment, not only in TBI but also in minor head trauma.

In a large study based in China, 855 patients (only 688 were included in the final analysis) who suffered from severe TBI were assessed for ∼5 years. The initial NLR was calculated, as was the follow-up until 1 year after the TBI or death, whichever came first. Unfavorable outcomes were reported in 73.8% of patients at the 1-year follow-up of head trauma. In this group, an NLR upon admission for severe TBI was associated with a worse clinical outcome. Sensitivity and specificity of elevated NLR in predicting a negative outcome at the 1-year follow-up were found to be 60.2 and 71.1%, respectively (34).

A recent study was conducted to assess the prognostic utility of hematological markers after TBI. This study took place in Western Australia and involved 388 patients who underwent decompressive craniectomy after severe TBI (33). Unfavorable outcomes at 18 months were reported in 38.9% of patients and found to correlate with hematological abnormalities such as hemoglobin level, disseminated intravascular coagulation score, plasma glucose level, activated partial thromboplastin time, international normalized ratio (INR), and fibrinogen. Interestingly, an increased NLR was not associated with an increase in the incidence of unfavorable outcomes at 18 months post-decompressive craniectomy after severe TBI. After adjusting for the predicted risk of the International Mission for Prognosis and Analysis of Clinical Trials (IMPACT), the study concluded that the INR was the best blood parameter for 18-month survival in patients with severe TBI undergoing decompressive craniectomy (33).

The peak of the NLR in patients with severe TBI has been studied to assess its utility in predicting 1-year outcomes. A 4-year study of 316 patients reported that 81.3% experienced unfavorable clinical outcomes. The peak of NLR was found to be an independent predictor of unfavorable outcomes following severe TBI. Furthermore, the NLR on day one and the initial GCS score were found to be independently correlated with increased peak NLR (23). A large study was completed on TBI that involved 1,291 patients. The factors that were found to be independent predictors of negative outcomes after 6 months were age and admission GCS scores along with the presence of subdural hematoma, intraparenchymal hemorrhage, traumatic subarachnoid hemorrhage, or coagulopathy (36).

Poor outcomes were associated with an increased NLR. When combined with certain standard prognostic factors such as age, GCS score, and coagulopathy, the NLR was reported to be capable of predicting the 6-month mortality more accurately (36).

Beyond the TBI, NLR was assessed in other neurological conditions, such as stroke. Khanzadeh et al. conducted a meta-analysis of 15 studies to evaluate using NLR to detect early poststroke infection (PSI) (48). They found significantly higher NLR levels in stroke patients with PSI compared to those without it (SMD = 0.98; 95% CI = 0.81–1.14; p < 0.001); however, the levels were comparable in terms of poststroke

![Comparison of neutrophil-lymphocyte ratio (NLR) in patients with favorable outcomes to those with unfavorable ones.](image-url)
Figure 3: Underlying pathophysiology of traumatic brain injury. DAMPs, Damage-associated molecular patterns; iNOS, inducible nitric oxide synthase; MP-TF, micro particles tissue factor; ROS, reactive oxygen species; SIRS, systemic inflammatory response syndrome; tPA, tissue plasminogen activator.
ventriculitis, sepsis, and urinary tract infections (48). In another
meta-analysis of 3641 acute ischemic stroke patients - who
received intravenous thrombolysis-, higher NLR levels were
linked to higher odds of hemorrhagic transformation (OR =
1.33; 95% CI = 1.14–1.56; p < 0.001) and poor 90-day
functional outcome (OR = 1.64; 95% CI = 1.38–1.94; p < 0.001)
(49). In the same context, stroke patients with early neurological
deterioration (END) had higher NLR levels than those without
END (SMD = 0.73; 95% CI = 0.42–1.05; p < 0.001) (50).

Despite the limited evidence about NLR in TBI patients,
our intellectual thoughts from the current evidence suggest
that an increased NLR ratio correlates with poor prognosis
in TBI patients. Nevertheless, the heterogeneity in the
included studies, in terms of measurement intervals, follow-
up points, and definitions of different outcomes, makes it
impossible to draw any concrete conclusions. Further trials
are needed to confirm the correlation between the NLR ratio
and prognosis.

Conclusions

A relatively inexpensive test, NLR can be easily and
rapidly obtained in the emergency department. In this
study, a high NLR at 24 and 48 h after TBI in pediatric
patients was associated with worse clinical outcomes. In
patients with minor TBI, the NLR was found to be an
important prognostic marker when used in conjunction
with head CT. NLR may be a useful predictor of the 6-
month and 1-year mortalities. However, the overwhelming
heterogeneity in current literature keeps the prognostic value
of the neutrophil-to-lymphocyte ratio for TBI outcomes under
investigation, and there are certainly more cost-effective and
quick approaches to predict TBI outcomes, such as Glasgow
Outcome Scale and Pupillary Light Reflex. Further studies
are warranted to confirm the utility of NLR in predicting
TBI outcomes.

Data availability statement

The original contributions presented in the study are
included in the article/Supplementary material, further inquiries
can be directed to the corresponding author/s.

Author contributions

All authors listed have made a substantial, direct,
and intellectual contribution to the work and approved it
for publication.

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Conflict of interest

KK was employed by Nested Knowledge.

The remaining authors declare that the research was
conducted in the absence of any commercial or financial
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Supplementary material

The Supplementary Material for this article can be
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