e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(11); 90-96

Original Research Article

# Red Blood Cell Distribution Width and Neutrophil-Lymphocyte Ratio as a Prognostic Biomarker for Mortality in Traumatic Brain Injury

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**Received: 10-07-2023 Revised: 16-08-2023 / Accepted: 25-09-2023**

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**Conflict of interest: Nil**

**Abstract**

**Aim:** The aim of the present study was to examine the role of RDW and neutrophil to lymphocyte ratio (NLR) in predicting the prognosis of patients with traumatic brain injury.

**Methods:** The target population in the present prospective study was patients with traumatic brain injury referred to the Department of Anesthesiology, Institute of Medical Sciences Banaras Hindu University, UP, India for 6 months. Using the random sampling method, a total number of 100 participants enrolled in the study.

**Results:** The mean age of the study population was 62.18 (± 15.05) years. The mean NLR ($p = 0.05$), neutrophil count ($p=0.04$), platelet count ($p = 0.05$), and NIHSS ($p<0.01$) had a significant difference. Hypertension and hyperlipidemia were the most and the least common underlying diseases among the participants, respectively. The mean of the variables by patients' outcome (death or recovery) was assessed and compared with a T-test between the two groups to investigate the effect of the variables on the mortality of patients. Higher NIHSS scores were statistically significant with death within three months ($p < 0.01$), while the higher neutrophil count was associated with higher survival ($p= 0.02$). The receiver operating characteristic (ROC) curve was utilized to compare the predictions of deaths by variables, including RBC, NIHSS, NLR, and RDW at the end of the 3-month follow-up. We found that the NIHSS (area under curve (AUC): 0.905).

**Conclusion:** Red cell distribution width is a predictor of mortality in patients with TBI. NLR is a reflection of the degree of the inflammatory response (neutrophils) and immune status (lymphocytes), which shows an increase in the recruitment of inflammatory cells and the release of inflammatory cytokines when NLR level increases. According to the results of the present study, it was suggested to increase the sample size in future studies to increase the accuracy of the results, control and delete other probable variables affecting RDW in the sample, including the information about the region and volume of hemorrhage and evaluate the relationship between study variables and the prognosis of patients in different age groups.

**Keywords**: Red cell distribution width, traumatic brain injury, Neutrophil to lymphocyte ratio, Prognosis



## Introduction

The injury to the brain results in activation of the inflammation cascade resulting in secondary insult, brain injury and negative outcomes. [1,2] There is increasing role of routine laboratory parameters in identifying and quantify neuroinflammation and systemic inflammation and thus predicting the outcome in various neurological disorders. [3-6] This has led to the need to identify reliable, accessible, and cost-effective biomarkers that can help predict the outcome following injury to the brain. [7] Many studies have explored the role of analysis of complete blood count (CBC) parameters to screen the inflammation and its impact on neurological outcomes. [7-10] The parameters of interest include a neutrophil-to-lymphocyte ratio (NLR), red cell width distribution (RDW) is a ratio of RBC distribution width (RDW) to platelet count and has been studied to correlate with reflecting the

severity of inflammation and prognostication in various diseases. [11,12]

Complete blood count is a laboratory test widely used in clinical practice and comprises. As a part of the complete blood count, red cell distribution width (RDW) is often used to differentiate the etiology of anemia. [13] Previous studies have indicated that the RDW was associated with mortality and other severe adverse outcomes of cardiovascular disease [14], severe acute pancreatitis (SAP) [15] and many other diseases. [16,17] Recent study exhibits that RDW may be a prognostic biomarker for mortality even for the general population. [18] There are few data on RDW in patients with traumatic brain injury (TBI). [19,20] In one study, no differences were found in RDW between surviving and non-surviving TBI patients. [19] Another study found higher RDW on admission in non-survivors than in surviving TBI patients [20]; however, a regression analysis was not carried out to establish an association between RDW and TBI mortality

Neutrophil to lymphocyte ratio (NLR) are indices that can represent the activities of the inflammatory complex and inflammatory responses in the vascular bed. [21] The NLR is a valuable biomarker for evaluation of inflammatory response following intracerebral hemorrhage (ICH), and it is associated with prognosis, in which the more severe the inflammatory response, the more aggravated nerve injury is expected. [22,23]

The aim of the present study was to examine the role of RDW and neutrophil to lymphocyte ratio (NLR) in predicting the prognosis of patients with traumatic brain injury.

## Materials and Methods

The target population in the present prospective study was patients with traumatic brain injury referred to the Department of Anesthesiology, Institute of medical sciences Banaras Hindu University, UP , India for 6 months. Using the random sampling method, a total number of 100 participants enrolled in the study.

Inclusion criteria-Traumatic brain injury diagnosis was based on the history and CT head finding of patient, patients with age of over 16-60 years will be included.

Exclusion criteria-Patients with severe multiple injury, visceral hemorrhage, anemia, cardiovascular disease, diabetes or with incomplete medical record was excluded.

For each patient with history of traumatic brain injury, a complete diagnostic work-up was performed. The information recorded includes demographics, etiology, Glasgow Coma Scale (GCS) scores and the 28-day mortality. The following laboratory measurers was obtained from each patient record on admission: RDW, Hemoglobin (Hb), and Hematocrit (Hct) and neutrophil, lymphocyte ratio. Blood Measurements -Venous blood (3 mL) was collected from patients presenting to the ICU. Complete blood count and red cell width was determined. NLR was calculated as a ratio of circulating neutrophil and lymphocyte counts. For continuous variables, paired t test was employed and for non-normal distribution Wilcoxon test was employed. For diagnostic and prognostic value receiver operating characteristic curve was used.

### Data Collection

Patient information, including age, gender, underlying dieases (e.g., hypertension, diabetes, hyperlipidemia, and ischemic heart disease), CBC parameters including white blood cell count, lymphocyte and neutrophil count, hemoglobin concentration, hematocrit, erythrocyte count, mean corpuscular hemoglobin concentration (MCHC), RDW and platelet count, neurological function and severity of the stroke measured using the National Institutes of Health Stroke Scale (NIHSS) score were collected. Moreover, mortality at discharge, within 28 days, and three months later were collected. NLR was calculated by dividing absolute neutrophil count to the absolute lymphocyte count.

### Outcomes

The primary outcome was to determine the relation- ship between RDW, NLR with the 3-month prognosis of participants. The secondary outcomes were to determine the RDW, NLR mean values in patients with TBI patients.

### Data Analysis

Collected data were analyzed by SPSS statistical analysis software version 18 (SPSS Inc., Chicago, IL, USA). First of all, the Smirnov-Kolmogorov test was used to assess the normal distribution of variables. Demographic variables were analyzed by descriptive statistical methods, and presented with percentage, frequency and mean ± standard deviation (SD). Analysis of quantitative variables was performed using independent sample T-test or Mann– Whitney U test. The p-values less than 0.05 were considered statistically significant.

## Results

**Table 1: Descriptive statistics of numerical variables**

| | Mean | Standard deviation |
|---|---|---|
| Age(year) | 62.18 | 15.05 |
| WBC (×1000) | 12.68 | 5.25 |
| Lymphocyte (%) | 16.64 | 10.40 |
| Neutrophil (%) | 76.84 | 15.90 |
| Hemoglobin (g/dl) | 12.78 | 2.68 |
| Hematocrit (%) | 42.18 | 5.58 |
| RBC (×1000000) | 4.76 | 0.679 |
| MCHC (g/dl) | 32.08 | 1.96 |
| RDW (%) | 13.90 | 1.5 |
| Platelet (×1000) | 234.860 | 66.84 |
| NIHSS | 15.86 | 15.09 |
| NLR | 8.22 | 6.24 |

The mean age of the study population was 62.18 (± 15.05) years. The mean NLR ($p = 0.05$), neutrophil count ($p=0.04$), platelet count ($p = 0.05$), and NIHSS ($p<0.01$) had a significant difference.

**Table 2: Descriptive statistics of categorical variables**

| Underlying disease | Number (%) | | | |
|---|---|---|---|---|
| | | Both sexes (n = 100) | Males (n = 55) | Females (n = 45) |
| Diabetes | Yes | 15 (15) | 7 (12.7) | 8 (17.77) |
| | No | 85 (85) | 48 (87.3) | 37 (82.22) |
| Hyperlipidemia | Yes | 6 (6) | 2 (3.64) | 4 (8.8) |
| | No | 94 (94) | 53 (96.36) | 41 (91.11) |
| Hypertension | Yes | 76 (76) | 37 (67.28) | 39 (86.66) |
| | No | 24 (24) | 18 (32.72) | 6 (13.34) |
| Coronary artery disease | Yes | 18 (18) | 12 (21.82) | 6 (13.34) |
| | No | 82 (82) | 43 (78.19) | 39 (86.66) |

Hypertension and hyperlipidemia were the most and the least common underlying diseases among the participants, respectively.

**Table 3: Comparison of the mean of research variables by 3-month prognosis of patients**

| Variables | 3-month prognosis | Number | Mean | Standard deviation | P (t-test) |
|---|---|---|---|---|---|
| NLR | Dead | 40 | 9.41 | 7.13 | 0.05 |
| | Alive | 60 | 7.43 | 5.58 | |
| RDW | Dead | 41 | 13.37 | 2.18 | 0.10 |
| | Alive | 59 | 12.78 | 1.95 | |
| NIHSS | Dead | 40 | 28.56 | 14.26 | 0.00 |
| | Alive | 60 | 7.85 | 9.31 | |
| Platelet | Dead | 44 | 219.64 | 56.78 | 0.04 |
| | Alive | 56 | 242.98 | 72.28 | |
| MCHC | Dead | 40 | 32.16 | 1.52 | 0.82 |
| | Alive | 60 | 32.08 | 2.16 | |
| RBC | Dead | 43 | 4.64 | 0.84 | 0.07 |
| | Alive | 57 | 4.84 | 0.56 | |
| WBC | Dead | 40 | 12.42 | 5.15 | 0.12 |
| | Alive | 60 | 12.08 | 5.35 | |
| Lymphocyte | Dead | 40 | 12.88 | 9.96 | 0.08 |
| | Alive | 60 | 16.94 | 10.60 | |
| Neutrophil | Dead | 40 | 81.69 | 12.88 | 0.02 |
| | Alive | 60 | 76.84 | 16.44 | |
| Hemoglobin | Dead | 40 | 14.46 | 2.46 | 0.22 |
| | Alive | 60 | 15.02 | 2.88 | |
| Hematocrit | Dead | 40 | 42.78 | 6.94 | 0.3 |
| | Alive | 60 | 44.46 | 4.36 | |

The mean of the variables by patients' outcome (death or recovery) was assessed and compared with a T-test between the two groups to investigate the effect of the variables on the mortality of patients. Higher NIHSS

scores were statistically significant with death within three months ($p < 0.01$), while the higher neutrophil count was associated with higher survival ($p= 0.02$).

**Table 4: Changes in parameters at from day 1 to day 7**

| Patient characteristics | At day 1 | Day 7 |
|---|---|---|
| Age | 62.18 ± 15.05 | |
| Hemoglobin | 12.78±2.68 | 11.48±3.16 |
| GCS | 12±3 | 8±4 |
| RDW | 13.9±1.5 | 14.00±3.10 |
| Neutrophil lymphocyte ratio | 8.22±6.24 | 9.31±5.45 |

RDW and Neutrophil lymphocyte ratio showed increase in value from day 1 to day 7.

**Table 5: Level below ROC diagram for research variables**

| Tested variables | Levels below the chart |
|---|---|
| RBC | 0.454 |
| RDW | 0.632 |
| NIHSS | 0.905 |
| NLR | 0.540 |

The receiver operating characteristic (ROC) curve was utilized to compare the predictions of deaths by variables, including RBC, NIHSS, NLR, and RDW at the end of the 3-month follow-up. We found that the NIHSS (area under curve (AUC): 0.905).

**Discussion**

Red cell distribution width (RDW) is a parameter that represents the dispersion of erythrocyte volume. Coefficient of size changes of red blood cells is more accurate than the structure of red blood cells in peripheral blood smears. [24,25] The RDW values can be determined easily using an automatic flow cytometer as part of a standard complete blood count (CBC). [26] Previous studies have shown that abnormal RDW values are highly associated with mortality and poor prognosis [27-28] in various diseases such as acute coronary syndrome, cerebral ischemic disease, heart failure, and peripheral vascular disease. [29-31] Higher RDW values impair blood circulation and oxygen supply, so elevated RDW values are associated with more severe and unfavorable outcomes.[32] Traumatic brain injury (TBI) causes worldwide concern, as one of the leading causes of mortality and morbidity,, especially in young and older adults. [33] However, few biomarkers were reported in clinical practice when evaluating the brain damage. Recent researchers found that protein S-100 beta (β), neuron-specific enolase (NSE), glial fibrillary acidic protein (GFAP) and myelin basic protein (MBP) etc. could be used as promising markers of TBI. [34,35] However, considering the convenience and operability of clinical practice, none of these could be easy and widely used prognostic biomarkers for TBI mortality evaluating.

The mean age of the study population was 62.18 (± 15.05) years. The mean NLR ($p = 0.05$), neutrophil count ($p=0.04$), platelet count ($p = 0.05$), and NIHSS ($p<0.01$) had a significant difference. Hypertension and hyperlipidemia were the most and the least common underlying diseases among the participants, respectively. The mean of the variables by patients' outcome (death or recovery) was assessed and compared with a T-test between the two groups to investigate the effect of the variables on the mortality of patients. Higher NIHSS scores were statistically significant with death within three months ($p < 0.01$), while the higher neutrophil count was associated with higher survival ($p= 0.02$). In our study, the role of the RDW factor in the prognosis and mortality of stroke patients with ICH in a period of three months was assessed, and it was shown that the RDW value is significantly higher in deceased patients compared to alive patients with ICH. The results of the study conducted by Lorente et al. among 117 patients with spontaneous ICH showed that RDW during the first week was higher in deceased than surviving patients ($p \leq 0.001$), which is in accordance with our findings. [36] Furthermore, the article by Kaya et al. conducted on 153 participants, concluded that RDW is an important hematopoiesis indicator for the occurrence of stroke in patients with heart failure, which reveals that high RDW is associated with the development of stroke and is strongly associated with cardiovascular causes. [32] A study by Moreno et al. also showed that RDW is a strong indicator for stroke. [37] Moreover, another study by Kara et al. concluded that RDW, an easily accessible and inexpensive test, is potentially an important parameter in diagnosing stroke and may predict prognosis. Also, in this study NIHSS was used to determine the severity of the stroke and it was found that the increase in stroke severity is associated with higher RDW, and RDW is a strong pre-dictor of the stroke severity. [38]

The receiver operating characteristic (ROC) curve was utilized to compare the predictions of deaths

by variables, including RBC, NIHSS, NLR, and RDW at the end of the 3-month follow-up. We found that the NIHSS (area under curve (AUC): 0.905). The NLR is calculated as dividing the number of neutrophils to the number of lymphocytes in peripheral blood and measures the inflammatory responses. [39] An acute inflammatory response occurs in severe conditions such as ischemic stroke, cerebral hemorrhage, and acute coronary syndrome. Therefore, this marker can deter- mine the prognosis and evaluation of disease outcomes in the mentioned diseases. [39,40] Numerous studies have shown that high levels of neutrophils are sensitive markers for determining mortality. [41] Jickling et al [42] and Maestrini et al [43] showed that high neutrophil level is associated with high infarct volume and poor prognosis.

## Conclusion

Red cell distribution width is a predictor of mortality in patients with TBI. NLR is a reflection of the degree of the inflammatory response (neutrophils) and immune status (lymphocytes), which shows an increase in the recruitment of inflammatory cells and the release of inflammatory cytokines when NLR level increases. According to the results of the present study, it was suggested to increase the sample size in future studies to increase the accuracy of the results, control and delete other probable variables affecting RDW in the sample, including the information about the region and volume of hemorrhage and evaluate the relationship between study variables and the prognosis of patients in different age groups.

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