

The role of TLC, RDW, and ESR in predicting short-term prognosis among admitted patients with acute ischemic stroke: Insights from a cross-sectional study

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Abstract

Background: Stroke is the third most common cause of disability and the second most common cause of death worldwide. Prognosis assessment in acute ischemic stroke is challenging for clinicians. The development of simple and easily performed prognostic markers that correlate with the outcome of patients can be of immense benefit. The aim of this study was to find out the prognostic significance of total leukocyte count, red cell distribution width and erythrocyte sedimentation rate in patients with acute ischemic stroke.

Methods: A descriptive cross-sectional study was conducted in a tertiary center after ethical approval from the Institutional Review Committee. The study period spanned from April 18, 2022 to June 17, 2023, a period of 14 months. 136 patients diagnosed with acute ischemic stroke with total leukocyte count (TLC), red cell distribution width (RDW), erythrocyte sedimentation rate (ESR), National Institutes of Health Stroke Scale (NIHSS), and modified Rankin Scale (mRS) were included in the study after fulfilling the inclusion criteria. The modified Rankin Scale (mRS) was obtained 28 days following admission. Data was collected and analyzed through Microsoft Excel 365 and SPSS version 22. Spearman Correlation and multivariate regression analysis were used to analyze the association.

Results: TLC, RDW, and ESR were significantly associated with an mRS at 28 days showing a positive correlation between them. Total in-hospital mortality has been significantly associated with TLC only ($p < 0.05$).

Conclusions: The prognostic value of TLC, RDW, and ESR in patients with acute ischemic stroke was found to be significant and similar to the studies done in similar settings.

KEYWORDS

acute ischemic stroke, hematological indices, inflammation, modified Rankin Scale, NIHSS, prognosis

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1 | INTRODUCTION

Cerebrovascular accidents (stroke) are the second leading cause of death and the third leading cause of disability worldwide.¹ World Health Organization (WHO) defines stroke as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 h or leading to death, with no apparent cause other than that of vascular origin.”² In Nepal, it is estimated that 50,000 people per year are afflicted with stroke, of which there are 15,000 annual deaths.³ By definition, stroke is clinically diagnosed, which is further supported by laboratory studies including brain imaging. Transient ischemic stroke is defined as all neurological signs and symptoms resolving within 24 h without evidence of brain infarction on brain imaging.⁴ When imaging or pathology is not available, clinical stroke is recognized by the persistence of symptoms for more than 24 h.⁵

Prognosis assessment in acute ischemic stroke (AIS) has been a challenge for clinicians.⁶ Computed tomography (CT) or magnetic resonance imaging (MRI) constitutes a strong predictor of clinical outcome in AIS. However, CT scan or MRI information concerning the extent of cerebral infarction is usually available too late to be of help. Also, these services are not easily available in most of the hospitals in developing and underdeveloped countries which makes the predictive value of neuroimaging limited to the long-term phase of stroke. So, the prediction of stroke outcomes basically relies on clinical findings.⁷

In resource rich settings, the prognosis of AIS is determined by various brain specific markers such as neuron specific enolase and glial fibrillary acidic protein.⁸ But these diagnostic tests are expensive as well as not easily available in resource-limited settings.

An important role is played by inflammation in the pathophysiology of cerebral ischemia. Fibrinogen, one of the acute phase reactant proteins has the greatest impact on erythrocyte aggregation, which is indirectly measured by erythrocyte sedimentation rate (ESR). Higher ESR indicates greater increase in fibrinogen levels and blood viscosity, leading to reduced cerebral blood flow. Many clinical research suggested increased ESR is associated with poor clinical outcomes, early clinical worsening and ultimately increased extend of brain damage.⁹ Leukocytes play a major role in inflammation following stroke.¹⁰ Increased recurrence of ischemic stroke was related to increased peripheral total leukocyte count (TLC) and neutrophil counts.¹¹ Several studies have shown TLC as a strong and independent indicator for severity of stroke.¹² According to the research by Gupta et al.,¹³ patients with ischemic stroke who had poor functional outcomes had higher levels of TLC ($p < 0.044$), blood glucose ($p < 0.002$), and CRP ($p < 0.003$). Increased inflammation have shown to decrease the survival of red blood cells, ultimately increasing red cell distribution width (RDW). RDW was comparable to tumor necrosis factor and C-reactive protein (CRP) in AIS, which are already established markers of inflammation.¹⁴

A large and diverse literature supports the view that the modified Rankin scale (mRS) is a valid and clinically relevant instrument for assessing recovery from stroke. This tool assesses the severity of stroke and measures the degree of disability in patients. It comprised six grades ranging from “no significant disability” to “death.” The mRS is heavily weighted towards global disability. The mRS exhibits a strong relationship with clinical measurements of stroke severity in addition to other disability and outcomes endpoints when properly administered.¹⁵ Clinical evolution during the first day of stroke and ESR are also independent predictors of short-term stroke outcome.⁷ In the study conducted by Balestrino et al.,¹⁶ the prognosis was significantly worsened by the measurement of an elevated ESR or TLC count. For TLC count, in the upper quartile of population (TLC count > 9600 cells/mm³), the risk of severe disability or death was scored 5 or 6 on the modified Rankin scale.¹⁶

No study has been done in Nepal so far about the prognostic value of routine hematological indices in the cases of stroke. So, this study would be helpful to determine the prognosis of AIS and plan further management.

1.1 | Objective

To study the association of TLC, RDW, and ESR levels with clinical severity following acute ischemic stroke.

2 | METHODS

2.1 | Study design and settings

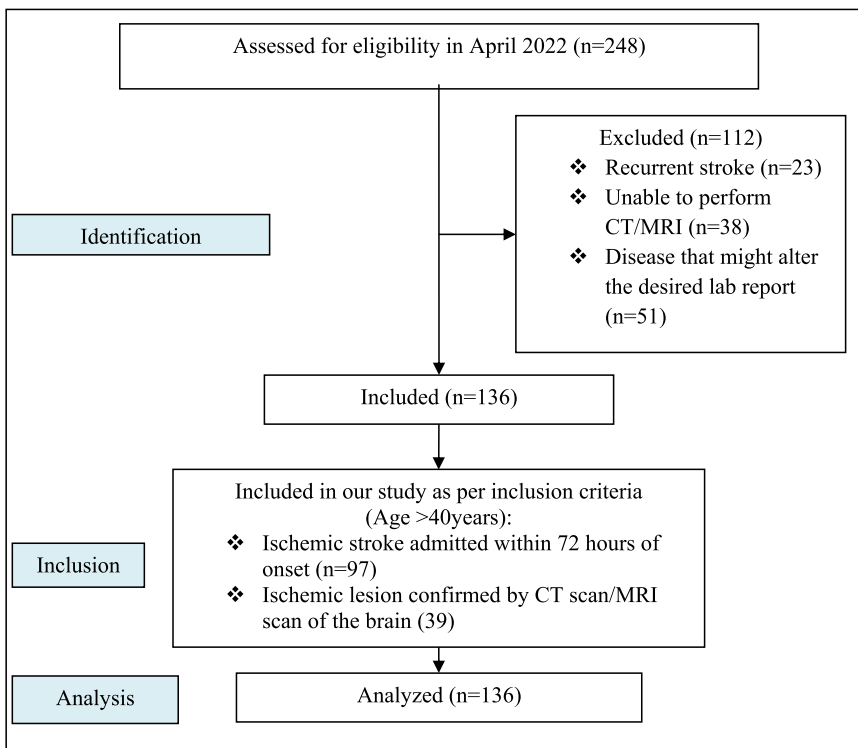
A descriptive cross-sectional study was conducted among patients admitted to the medicine ward with clinical and radiological evidence of ischemic stroke in Nepalgunj Medical College and Teaching Hospital (NGMCTH). The study period spanned from April 18, 2022 to June 17, 2023, a period of 14 months.

National Institutes of Health Stroke Scale (NIHSS) score, TLC, RDW, and ESR were calculated within 24 h after the patients were admitted. The mRS score was obtained at 28 days after the admission. Patients who were discharged before 28 days were called to the OPD for follow up. The study's reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology statement, as shown in a flow chart in Figure 1.

2.2 | Ethics

This study received ethical approval from the Institutional Review Committee of Nepalgunj Medical College and Teaching Hospital (NGMCTH) (Ref. 507/078-079) on Feb 16, 2022. The confidentiality of all the participants was taken in account. All the participants gave a

FIGURE 1 Strengthening the Reporting of Observational studies in Epidemiology (STROBE) for observational studies flow diagram. CT, computed tomography; MRI, magnetic resonance imaging.



written consent for the study and for those who were unable, immediate family members gave the written consent during first day of admission.

2.3 | Sample size determination and sampling technique

The sample size for the study was determined manually using a single proportion formula. Using the single population proportion formula, with assumptions; 50% of sample proportion (p) while using a cross-sectional study design, 10% margin of error (d), and $Z_{\alpha/2} = 1.96$, $n =$ required sample size;

$$n = (Z_{\alpha/2})^2 pq / d^2$$

$$n = (1.96)^2 0.5(0.5) / (0.1)^2$$

$$n = 96$$

Nonrandom (convenience) sampling method was applied to take the data from 136 patients presented with AIS.

2.4 | Eligibility criteria

Inclusion criteria:

- Cases of ischemic stroke admitted within 72 h of onset, the diagnosis of stroke being established by the WHO definition of stroke.
- Ischemic lesion confirmed by CT scan/MRI scan of brain or hemorrhage ruled out by CT scan.

- Age >40 years with the diagnosis of stroke.

Exclusion criteria:

- Patients with diseases and medical conditions (recent clinical infection, concurrent major renal, hepatic disease, recent surgery or major trauma, acute osteoarthritis, inflammatory disease, intracranial space-occupying lesion, or metabolic disturbances) that might substantially affect the levels of TLC, RDW, and ESR.
- Recurrent stroke.
- Patients in whom CT or MRI could not be done due to any reason.

Data were collected using a proforma in printed form that included detailed clinical history and physical examination and filled up by clinician.

2.5 | Statistical analysis

Collected data were entered in Microsoft Excel. Data were then analyzed statistically using Statistical Package for Social Sciences (SPSS Version 2022). The data were not normally distributed and the normality of data was tested using the Shapiro-Wilk test. The multivariate linear regression was used to see the correlation between TLC, RDW, and ESR with mRS. Multivariate analysis was done to determine the presence of a statistically significant association between independent variables and the dependent variable at 0.05 along with a 95% confidence interval (CI). A similar association was observed for the NIHSS and mRS. The evaluated data were presented in the form of tables and the association was considered to be significant if the p -value was less than 0.05.

3 | RESULTS

Out of 136 participants included in the study, 76 (55.9%) were male patients and 60 (44.1%) were female patients in total with the mean age of patients being 61.84 years (Table 1). Most of the patients belonged to the age group of 56–60 years followed by the age group of 70–75 years (Figure 2). Hypertension was the most prevalent risk factor (Figure 3). Out of 136 patients, 47.05% had multiple risk factors, 44.85% had a single risk factor and 8.09% did not have any known risk factors.

Hemiplegia/hemiparesis was the most common presentation followed by speech abnormality during admission with acute ischemic stroke (AIS) (Figure 4). The mean systolic blood pressure (BP) at the time of presentation was 143.31 (SD 31.013), and the mean diastolic BP was 87.53 (SD 16.730). The blood level of total cholesterol was 177.49 (SD 46.032), the mean high-density

cholesterol was 42.15 (SD 10.049), the mean low-density cholesterol was 100.27 (SD 38.663), and the mean triglycerides was 154.70 (SD 68.341) (Table 1). About 44.1% of patients presented with severe stroke, 6.6% with moderate to severe stroke, 34.6% with moderate stroke, and 14.7% with minor stroke according to NIHSS score. 79 (58.1%) out of a total of 136 patients have a $TLC \leq 11,000/\text{mm}^3$, 76 (55.9%) have $RDW \leq 13.5$, and only 14 (10.3%) have $ESR \leq 9$ as within the normal range.

The normality of data distribution was tested using the Shapiro–Wilk test. Our data were non-normal in distribution. Spearman's Correlation test was used to see the correlation between TLC and mRS, which had a positive correlation, meaning that patients who had higher TLC had worse functional status ($p < 0.001$) (Table 2). Similarly, RDW and mRS had a positive correlation stating patients with higher RDW had worse functional status ($p < 0.001$) (Table 3). ESR also showed a positive correlation, stating the fact that the higher the value of ESR, the worse would be the functional status of the patient ($p < 0.001$) (Table 4).

Strong positive correlation was observed between NIHSS score at admission and mRS scores at 28 days ($r = 0.92$; $p < 0.001$) (Figure 5). The baseline NIHSS score was predictive of the overall functional outcome at 28 days.

To identify the predictive potential of TLC, RDW, and ESR for mRS at 28 days, the multivariate linear regression analysis was performed. The model adjusted for TLC, RDW, ESR, age, sex, NIHSS, hypertension, diabetes, coronary artery disease, dyslipidemia, and smoking was taken into account. Analysis results demonstrated that TLC (95% CI, 0.000–0.000; $p < 0.018$), RDW (95% CI, 0.038–0.275; $p < 0.010$), ESR (95% CI, 0.001–0.019; $p < 0.026$), and NIHSS (95% CI, 0.090–0.112; $p < 0.000$) were significant for mRS at 28 days (Table 5).

Total in-hospital mortality was four during the hospitalization period. The chi-square test was used to see the association between TLC and mortality, which showed a significant association with mortality (p -value < 0.05), but no such association was found with RDW and ESR (Table 6).

TABLE 1 Baseline characteristics of the patients ($n = 136$).

| Variables | N | Mean | Std. deviation |
|-------------------|--------|----------------|----------------|
| Mean age | | 61.84 ± 12.017 | |
| Sex | Male | 76 (55.9%) | |
| | Female | 60 (44.1%) | |
| SBP | 136 | 143.31 | 31.013 |
| DBP | 136 | 87.53 | 16.730 |
| RBG | 136 | 117.02 | 43.982 |
| Total cholesterol | 136 | 177.49 | 46.032 |
| HDL | 136 | 42.15 | 10.049 |
| LDL | 136 | 100.27 | 38.663 |
| TGs | 136 | 154.70 | 68.341 |

Abbreviations: DBP, diastolic blood pressure; HDL, high-density cholesterol; LDL, low-density cholesterol; RBG, random blood glucose; SBP, systolic blood pressure; TGs, triglycerides.

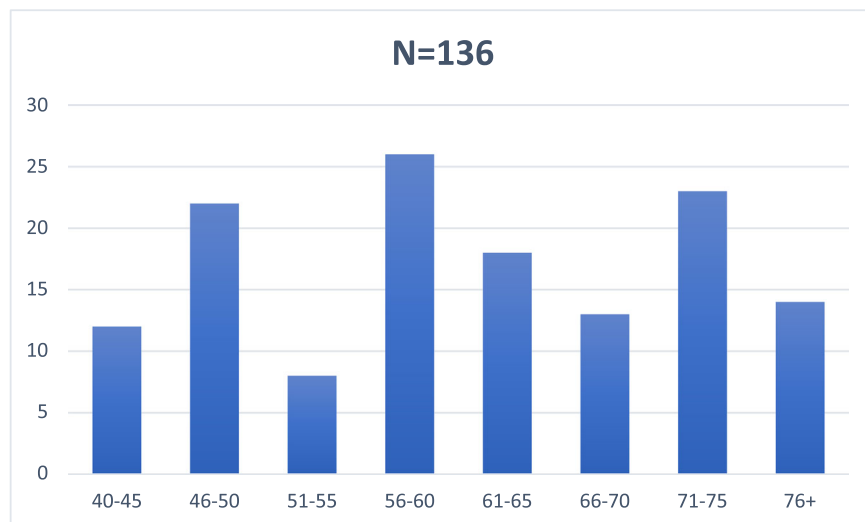


FIGURE 2 Age-wise distribution of study population.

FIGURE 3 Prevalence of risk factors presenting with acute ischemic stroke.

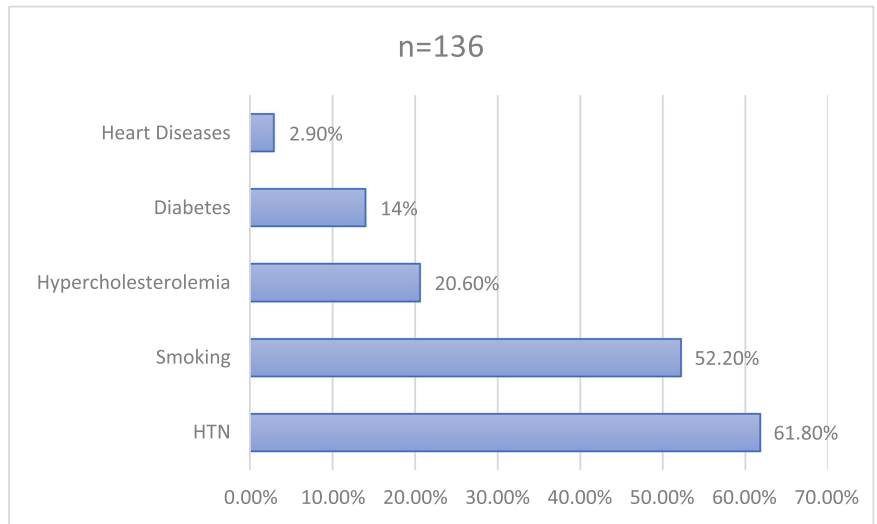


FIGURE 4 Clinical presentation of patients with acute ischemic stroke.

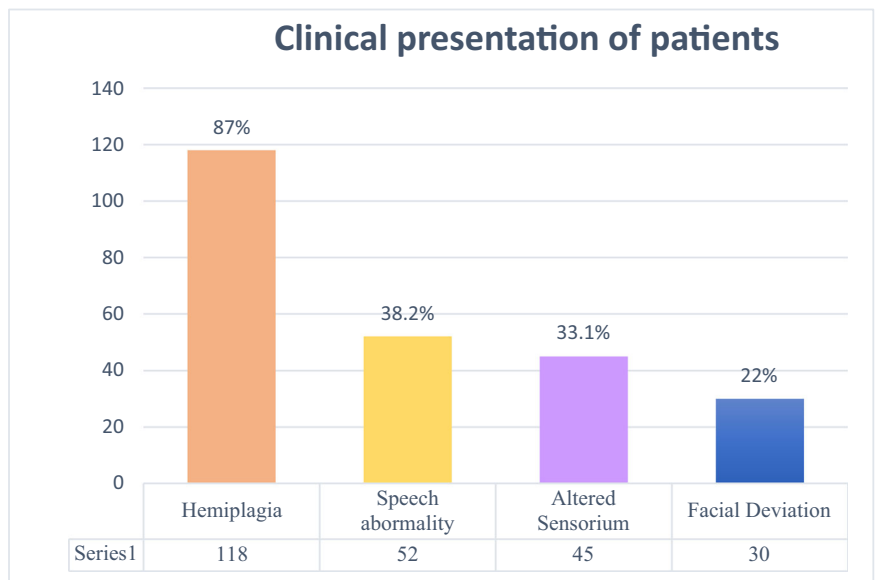


TABLE 2 Association of TLC with mRS.

| mRS | mRS of patients with TLC ≤ 11,000 | mRS of patients with TLC > 11,000 | p-Value |
|--------------------|-----------------------------------|-----------------------------------|---------|
| 0 | 7 | 0 | <0.001 |
| 1 | 12 | 1 | |
| 2 | 26 | 8 | |
| 3 | 14 | 14 | |
| 4 | 12 | 19 | |
| 5 | 8 | 11 | |
| 6 | 0 | 4 | |
| Total participants | 79 | 57 | |

Abbreviations: mRS, modified Rankin Scale; TLC, total leukocyte count.

TABLE 3 Association of red cell distribution width (RDW) with modified Rankin Score (mRS).

| mRS | Frequency of mRS with RDW | | p-Value |
|--------------------|---------------------------------|---------------------------------|---------|
| | mRS of patients with RDW ≤ 13.5 | mRS of patients with RDW > 13.5 | |
| 0 | 7 | 0 | <0.001 |
| 1 | 13 | 0 | |
| 2 | 19 | 15 | |
| 3 | 18 | 10 | |
| 4 | 14 | 17 | |
| 5 | 4 | 15 | |
| 6 | 1 | 3 | |
| Total participants | 76 | 60 | |

4 | DISCUSSION

There were 76 (55.9%) male patients and 60 (44.1%) female patients with the male-to-female ratio of 1.27:1; a prevalence study done in Bangladesh had a male-to-female ratio of 1.43:1.¹⁷ The age distribution of patients with stroke varied from 40 years to 87 years of age, with the mean age of patients being 61.84 years. A study conducted at Nepal Medical College in Kathmandu showed a mean age at presentation of 61.65 years, which was comparable with our study, and 58.3% were male and 41.7% were female.¹⁸ In our study, 87% of patients had hemiplegia or hemiparesis at presentation. Speech abnormality, either aphasia or dysarthria, was present in 38.2% of the patients. Other symptoms at presentation were loss of consciousness or altered sensorium which were present in 33.1% of patients and 22.1% had facial weakness. None of the patients had sensory symptoms in our study. In a study conducted by Devkota et al 90.3% of patients had limb weakness, 22.2% of cases had facial deviation, 33.3% had slurring of speech, and 29% of patients had altered sensorium at the time of presentation.¹⁸

Leukocytosis was found in 41.9% of AIS patients in our study. This observation is supported by a study by Nikanfar et al.,¹⁹ which stated that 46.7% of the patients had leukocytosis. Our study showed that patients with TLC in the lower range had less severe

disability at presentation and a gradual improvement in functional status than patients with TLC in the higher range. There was an improvement from Grade 3 to Grade 2, from moderate disability to slight disability, according to mRS. The result of our study was similar to that of Nardi et al.,²⁰ who found a strong correlation between a higher leukocyte count and the disability at discharge using the Spearman rank correlation ($r = 0.21$; $p < 0.001$). A study carried out in China by Peng et al.²¹ had similar outcomes. The study came to the conclusion that leukocytosis at admission was significantly associated with in-hospital mortality and with dependency at discharge.²¹

Our study showed that patients with a higher RDW value had a severe disability, and there was less improvement in functional status according to mRS at 28 days. The correlation using multivariate regression analysis model was statistically significant in our study ($p < 0.05$). These findings were similar to a study done by Kara et al.,²² which concluded there is a statistically significant correlation between RDW at the time of admission and stroke severity with $p < 0.009$. Study done by Mohindra et al.²³ showed similar results, indicating a higher RDW index has a statistically significant correlation with the severity of AIS.

A similar correlation was found with ESR and mRS at 28 days in our study and it was statistically significant in our study ($p < 0.026$). A study done by Nikanfar et al.¹⁹ in 2012 had similar results, a fair and meaningful correlation between in-admission serum ESR level and in-admission mRS ($p < 0.001$, $r = 0.446$) and a strong and meaningful correlation between in-admission ESR level and mRS while releasing from the hospital ($p < 0.001$, $r = 0.508$).

During our study period, there was mortality in four patients between Day 4 and Day 7 of the presentation. All those patients who lost their lives had a large MCA territory infarction. There were a few limitations to the study. We did not have information on long-term outcomes because long-term follow-up was not

TABLE 4 Association of ESR with mRS.

| mRS score | 0 | 1 | 2 | 3 | 4 | 5 | 6 |
|-----------------|--------|---|----|----|----|----|---|
| ESR ≤ 9 | 4 | 5 | 4 | 1 | 0 | 0 | 0 |
| ESR > 9 | 3 | 8 | 30 | 27 | 31 | 19 | 4 |
| <i>p</i> -Value | <0.001 | | | | | | |

Abbreviations: ESR, erythrocyte sedimentation rate; mRS, modified Rankin Score.

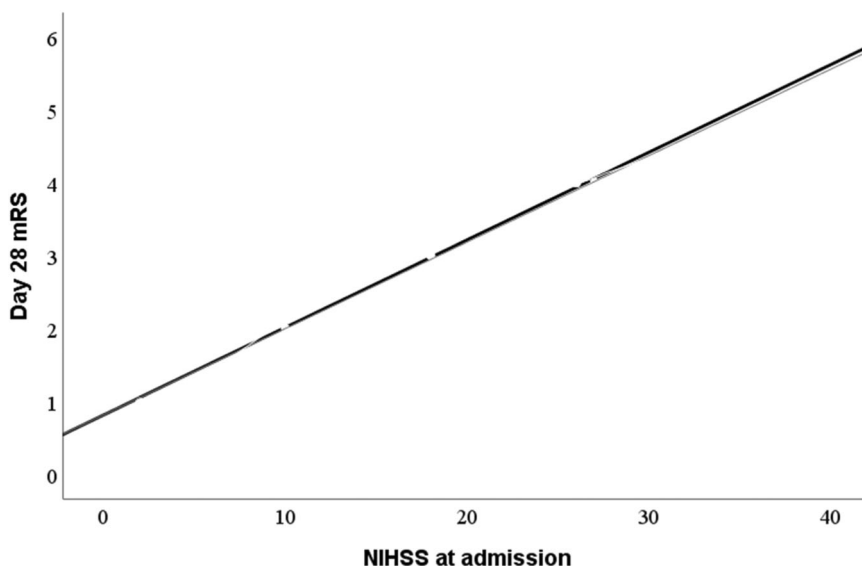


FIGURE 5 Correlation of the presenting National Institutes of Health Stroke Scale (NIHSS) score and the modified Rankin score (mRS) (at 28 days). The regression line is obtained by plotting the fitted values of 28-day mRS scores and the NIHSS at admission.

TABLE 5 Predictors of mRS at 28 days in multivariate linear regression analysis.

| Coefficients | | Unstandardized coefficients | | Standardized coefficients | t | Sig. | 95% CI |
|--------------|--------------|-----------------------------|------------|---------------------------|--------|-------|------------------|
| | | B | Std. error | β | | | |
| Model 1 | (Constant) | -4.152 | 1.296 | | -3.203 | 0.002 | -6.716 to -1.587 |
| | TLC | 0.000 | 0.000 | 0.310 | 4.868 | 0.000 | 0.000-0.000 |
| | RDW | 0.338 | 0.103 | 0.217 | 3.287 | 0.001 | 0.135-0.542 |
| | ESR | 0.052 | 0.007 | 0.456 | 7.093 | 0.000 | 0.038-0.067 |
| Model 2 | (Constant) | -2.219 | 0.705 | | -3.147 | 0.002 | -3.614 to -0.823 |
| | TLC | 0.000 | 0.000 | 0.088 | 2.405 | 0.018 | 0.000-0.000 |
| | RDW | 0.156 | 0.060 | 0.100 | 2.608 | 0.010 | 0.038-0.275 |
| | ESR | 0.010 | 0.005 | 0.089 | 2.258 | 0.026 | 0.001-0.019 |
| | Age | 0.008 | 0.004 | 0.063 | 1.790 | 0.076 | -0.001 to 0.016 |
| | Sex | 0.147 | 0.095 | 0.050 | 1.546 | 0.125 | -0.041 to 0.334 |
| | NIHSS | 0.101 | 0.006 | 0.781 | 18.070 | 0.000 | 0.090-0.112 |
| | Hypertension | -0.025 | 0.103 | -0.008 | -0.247 | 0.806 | -0.228 to 0.178 |
| | Diabetes | -0.100 | 0.139 | -0.024 | -0.718 | 0.474 | -0.374 to 0.175 |
| | CAD | -0.326 | 0.291 | -0.038 | -1.121 | 0.264 | -0.902 to 0.250 |
| | Dyslipidemia | 0.092 | 0.119 | 0.025 | 0.774 | 0.440 | -0.144 to 0.328 |
| | Smoking | -0.065 | 0.095 | -0.022 | -0.682 | 0.496 | -0.254 to 0.124 |

Model 1: Adjusted for TLC, RDW, and ESR.

Model 2: Adjusted for TLC, RDW, ESR, age, sex, NIHSS, hypertension, diabetes, CAD, dyslipidemia, and smoking.

Abbreviations: CAD, coronary artery disease; CI, confidence interval; ESR, erythrocyte sedimentation rate; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; RDW, red cell distribution width; TLC, total leukocyte count.

TABLE 6 Association of TLC, RDW, and ESR with mortality.

| Mortality | TLC | | | RDW | | | ESR | | |
|-----------|---------------|------------|---------|-------------|----------|---------|----------|-------|---------|
| | $\leq 11,000$ | $> 11,000$ | p-Value | ≤ 13.5 | > 13.5 | p-Value | ≤ 9 | > 9 | p-Value |
| No | 79 | 53 | | 75 | 57 | | 14 | 118 | |
| Yes | 0 | 4 | <0.05 | 1 | 3 | 0.2 | 0 | 4 | 0.6 |

Abbreviations: ESR, erythrocyte sedimentation rate; RDW, red cell distribution width; TLC, total leukocyte count.

done. It was a single-center study with a small sample size done in a short period of time.

4.1 | Limitations of the study

The sample was taken from the study population admitted to NGMCTH. These findings cannot be generalized to other hospitals or settings. Further large-scale studies are advised to uncover the effect of such hematological factors on the prognosis of stroke in patients admitted to the hospital. Due to the use of mRS which has the potential for interobserver variability, in our study, there could be the presence of observer bias.

5 | CONCLUSIONS

Estimating hematological indices is a simple and safe laboratory test that is offered at the majority of institutes in Nepal. It could be an important test for assessing the prognosis of AIS patients. This study discovered a strong correlation between the clinical outcomes in AIS patients as measured by mRS and the routine hematological indices. Raised hematological indices were closely associated with patients' poor functional status. There was a mortality rate of four patients during the period of hospitalization. All of these patients had large infarctions involving the middle cerebral artery territory. So, the size of the infarction also should be kept in consideration during the treatment of AIS patients. Our study highlights the significance of

measuring routine hematological indices in AIS patients and implies that these indices have a significant role in the treatment and prognosis of AIS patients.

AUTHOR CONTRIBUTIONS

Rupak KC: Methodology; software; writing—review & editing; writing—original draft. **Birendra Kumar Yadav:** Supervision; investigation; resources. **Birat Basnet:** Project administration; resources; writing—review & editing. **Anjali Basnet:** Resources; data curation; project administration.

ACKNOWLEDGMENTS

There had been no funding support for this research.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in Figshare at [doi:10.6084/m9.figshare.25442425.v1](https://doi.org/10.6084/m9.figshare.25442425.v1).

TRANSPARENCY STATEMENT

The lead author Suman KC affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: KC S, KC R, Yadav BK, Basnet B, Basnet A. The role of TLC, RDW, and ESR in predicting short-term prognosis among admitted patients with acute ischemic stroke: insights from a cross-sectional study. *Health Sci Rep*. 2024;7:e2168. doi:10.1002/hsr2.2168