ORIGINAL RESEARCH

Association Between NLR, MLR and Stroke Incidence, All-Cause Mortality Among Low-Income Aging Populations: A Prospective Cohort Study

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Objective: This study aimed to assess the association of the Neutrophil-to-Lymphocyte Ratio (NLR) and Monocyte-to-Lymphocyte Ratio (MLR) in predicting stroke incidence and all-cause mortality in low-income elderly populations.

Methods: This prospective cohort study included participants who were middle-aged or elderly individuals from a low-income population in China. Participants were selected into the cohort and complete baseline assessments, which included questionnaire surveys, physical examinations, blood tests, and carotid artery ultrasound evaluations. Cox proportional hazards regression analysis was used to assess the associations of the NLR and MLR with the incidence of stroke and all-cause mortality. The predictive performance of the model was evaluated using the area under the receiver operating characteristic curve (AUC-ROC).

Results: A total of 3948 participants were enrolled in the study. Over a median follow-up period of 7 years, 262 participants experienced stroke events and 227 participants died. After adjusting for potential confounding variables, the final model revealed that a higher NLR was significantly associated with an increased risk of stroke (HR: 1.776, 95% CI: 1.250–2.254, P = 0.001) and all-cause mortality (HR: 1.558, 95% CI: 1.148–2.116, P = 0.004). Furthermore, a higher MLR was found to be associated with an increased risk of all-cause mortality (HR: 1.397, 95% CI: 1.054–1.852, P = 0.020), but no significant association was observed between MLR and stroke incidence. ROC analysis revealed that the AUC for NLR in predicting stroke was 0.55 (95% CI: 0.52–0.59, P=0.005), while the AUC for MLR was 0.58 (95% CI: 0.54–0.62, P<0.001). Similarly, the AUC for NLR in predicting all-cause mortality was 0.57 (95% CI: 0.53–0.61, P<0.001), and the AUC for MLR was 0.61 (95% CI: 0.57–0.65, P<0.001).

Conclusion: These findings indicate that NLR is associated with an increased risk of stroke and all-cause mortality, while higher MLR is associated with all-cause mortality but not with stroke incidence. However, the modest predictive performance of both markers suggests that their clinical utility remains limited. Further research is needed to validate these associations and explore their potential role in comprehensive risk assessment models.

Keywords: NLR, MLR, stroke, all-cause death, low-income population, elderly populations

Introduction

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) identified stroke, a common form of cerebrovascular disease, is the leading cause of mortality and disability worldwide.[1] In 2016, stroke accounted for 5.5 million deaths and 116.4 million disability-adjusted life-years (DALYs) globally. The total number of stroke survivors reached 80.1 million, with 13.7 million new cases reported annually.[2] This burden is particularly pronounced in China, where over two million new stroke cases are recorded each year, and stroke is associated with the highest number of DALYs lost for any disease in the country.[3]

Similar situations also occur in other economically underdeveloped regions and countries.[4] Moreover, the economic costs of treatment and post-stroke care place significant strain on the healthcare system, society, and families. These challenges highlight the urgent need for the development of low-cost predictors for stroke risk.

Inflammation plays a crucial role in the development and progression of atherosclerosis and cardiovascular disease.[5] Several prospective studies have demonstrated that the ratio of white blood cells to their components serves as a readily available and cost-effective inflammatory biomarker with significant prognostic value in cardiovascular disease, chronic kidney disease, critical illnesses and all-cause mortality.[6,7] However, whether these leukocyte-related inflammatory markers are associated with stroke incidence and all-cause mortality in middle-aged and elderly people remains limited, especially in economically underdeveloped regions.

Inflammation is also reported to be a key factor in the pathogenesis of stroke and other cerebrovascular diseases. It plays a dual role in the acute and chronic phases of these diseases. In the acute phase, the inflammatory process is triggered by ischemia or vascular injury, leading to the activation of endothelial cells, platelets, and leukocytes. This response leads to the release of proinflammatory cytokines, chemokines, and adhesion molecules, which lead to blood-brain barrier disruption, leukocyte infiltration, and secondary brain damage.[8,9] In the chronic phase, persistent low-grade inflammation exacerbates atherosclerosis and plaque instability, which are the main causes of ischemic stroke. Elevated inflammatory markers, such as C-reactive protein (CRP), interleukin 6 (IL-6), and fibrinogen, are associated with increased stroke risk and poor prognosis in patients.[8,9] In addition, systemic inflammation is associated with vascular cognitive impairment and progression of recovery after stroke.[10–13] Understanding the interplay between inflammation and cerebrovascular disease provides opportunities for therapeutic intervention as well as prognostication. A study showed that NLR is an important risk factor for all-cause mortality and cardiovascular mortality in patients with cardiovascular disease.[14] Wang et al showed that NLR is an important indicator to assess the risk of death in people with metabolic syndrome.[15] Zhu et al showed that NLR and MLR have clinical value for predicting short-term outcomes in patients with acute ischemic stroke.[16] However, previous studies lack a focus on rural low-income populations.

Since people living in countries with low income, poor medical care, and socioeconomic underdevelopment are at greater risk of cerebrovascular disease and other diseases, it is of great significance to identify the relationship between these readily available and inexpensive inflammatory markers and the incidence of cerebrovascular disease and thus prevent occurrence of stroke.

Previous studies have shown that the NLR and MLR have the potential to identify individuals at high risk for various diseases. Current study employed a prospective design to investigate the relationship between lymphocyte-related inflammatory markers (NLR and MLR) and the risks of stroke and all-cause mortality among middle-aged and elderly populations in rural China. Additionally, we evaluated the predictive value of these markers in assessing the risk of cerebrovascular diseases, particularly stroke, as well as overall mortality in this population.

Methods

Study Population and Design

A longitudinal population-based cohort study was conducted in rural areas of Tianjin, China, using data from the Tianjin Brain Study, previously detailed in the literature.[17] The study was situated in a township comprising 18 administrative villages in Jizhou District, Tianjin. Approximately 95% of the population were low-income farmers, with a per capita disposable income of <1600 USD in 2014, the median of education was 6 years. Baseline data for this cohort were collected in 2016, 2018, and 2019, respectively. Participants were eligible for inclusion if they were aged ≥45 years local

residents, participated the physical examination. Those participants with the previous CVD (including coronary heart disease and myocardial infarction) or stroke (including ischaemic and hemorrhagic stroke) were excluded in this study.

This study adhered to the principles of the Declaration of Helsinki and was approved by the Tianjin Medical University General Hospital Ethics Committee (Approval No. [IRB2018-099-01]). A written informed consent was obtained from all participants.

Data Collection and Grouping
The data collection process encompassed demographic details, medical history, lifestyle factors, physical examinations, and laboratory tests (Supplementary Table).

Demographic Characteristics
Demographic variables included sex, age, and education level. Age was categorized into four groups: 45–54 years, 55–64 years, 65–74 years, and ≥75 years. Education levels were grouped into three categories: illiterate, 1–6 years of schooling, and >6 years of schooling.

Medical History
Participants reported their history of hypertension, diabetes, myocardial infarction, and stroke.

Lifestyle Information
Lifestyle factors included smoking and alcohol consumption. Smoking status was divided into: Never smokers, Former smokers (Those who had quit smoking for at least one-year)., Current smokers (Individuals who smoked one or more cigarettes daily for at least six months). Alcohol consumption was grouped as: Never drinkers, Former drinkers, Current drinkers (Those who consumed more than 500 g of alcohol per week for at least one year).

Physical Examinations
Measurements included height, weight, waist circumference, hip circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. Body mass index (BMI) was calculated and participants were categorized as: Normal weight: BMI of 18.5–24 kg/m², Overweight: BMI of 24–28 kg/m², Obese: BMI ≥28 kg/m².

Laboratory Tests
Blood samples were analyzed for: Complete blood count (CBC), Total cholesterol (TC), Triglycerides (TG), High-density lipoprotein cholesterol (HDL-C), Low-density lipoprotein cholesterol (LDL-C) and Fasting blood glucose (FBG). These baseline measurements were used to assess the participants' health status and inflammatory levels at the start of the study.

Calculation of NLR and MLR
The NLR was calculated as the ratio of the peripheral neutrophil count (N) to the lymphocyte count (L). Similarly, the MLR was determined as the ratio of the peripheral monocyte count (M) to the lymphocyte count (L).

Determination of Endpoints and Follow-up
The primary endpoint of the study was a composite outcome comprising all-cause mortality and nonfatal stroke events, including both nonfatal ischemic and hemorrhagic strokes. The follow-up period ended at the occurrence of either a stroke event or death from any cause. In cases where multiple events occurred, the most severe outcome was prioritized, with death being considered more severe than stroke.

Statistical Analysis
Continuous variables, such as age, BMI, education level, SBP, DBP, NLR, and MLR, were expressed as mean ± standard deviation (SD) or as median with interquartile range (IQR), depending on their distribution. Comparisons between two groups were performed using Student's *t*-test for normally distributed data or the Mann–Whitney *U*-test for non-normally distributed data. Categorical variables, including sex, age group, education level, BMI category, smoking status, alcohol

consumption, and histories of hypertension and diabetes, were presented as absolute numbers (percentages). Differences in categorical variables between groups were analyzed using the chi-squared test.

Receiver operating characteristic (ROC) curves were employed to determine cutoff values, with the optimal thresholds derived using Youden's index (sensitivity + specificity − 1). Lymphocyte-based inflammatory indices (NLR and MLR) were analyzed as categorical variables based on these optimal cutoff values.

Cox proportional hazards regression analysis was conducted to assess the associations of NLR and MLR with stroke incidence and all-cause mortality, adjusting for confounders such as age, sex, education level, BMI, diabetes, hypertension, smoking, alcohol consumption, and TC levels. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Statistical significance was defined as $P < 0.05$.

Data analyses were performed using GraphPad Prism (version 8.0.1; GraphPad Software, USA) and SPSS (version 25.0; SPSS Inc., Chicago, IL, USA).

Results

Total of 5023 residents were recruited in this cohort during the study periods. After exclusion the individuals who have the previous CVD (n=720) or stroke history (n=355), 3948 participants were analysed in this study finally (Figure 1).

Characteristics of the Study Population

Current study included 3948 participants with a median follow-up duration of 7 years. The mean age of participants was 60.25 ± 9.84 years, with 1762 (44.6%) being male. The average educational attainment was 5.49 ± 3.51 years, and the mean BMI was 25.44 ± 6.70 kg/m². Among the cohort, 24.8% were current smokers, 25.0% were current alcohol drinkers, and 63.4% were classified as overweight or obese. Hypertension was present in 67.2% of participants, and 15.1% had diabetes. Biochemical measurements revealed sex-specific differences: female participants had higher mean levels of total cholesterol (TC: 5.14 ± 2.13 mmol/L vs 4.79 ± 0.94 mmol/L), triglycerides (TG: 1.68 ± 1.46 mmol/L vs 1.57 ± 2.35 mmol/L), high-density lipoprotein cholesterol (HDL-C: 1.42 ± 0.40 mmol/L vs 1.40 ± 0.54 mmol/L), and low-density lipoprotein cholesterol (LDL-C: 2.95 ± 0.97 mmol/L vs 2.74 ± 0.77 mmol/L). Conversely, male participants had higher mean values for neutrophil-to-lymphocyte ratio (NLR: 2.01 ± 2.03 vs 1.73 ± 0.84) and monocyte-to-lymphocyte ratio (MLR: 0.23 ± 0.10 vs 0.20 ± 0.08).

During the 7-year follow-up period, 262 participants experienced stroke events, comprising 239 ischemic strokes and 23 hemorrhagic strokes, while 227 participants died (Table 1).
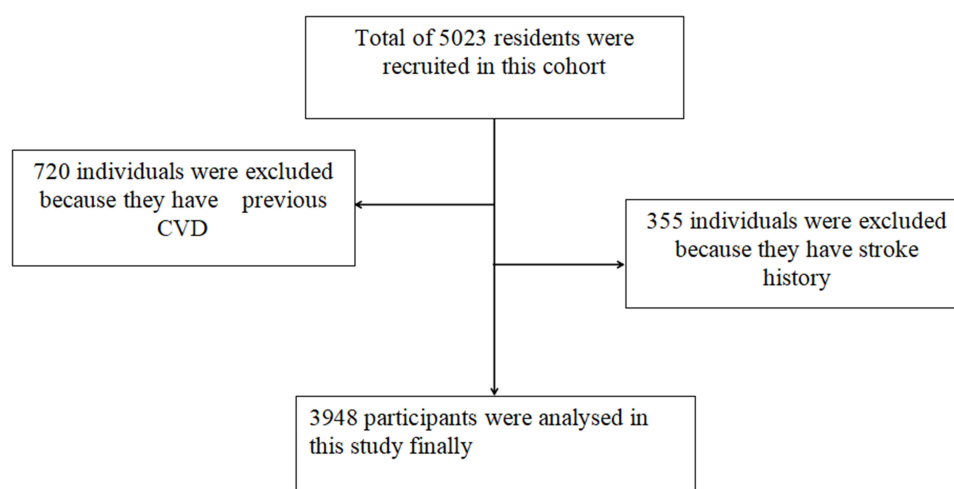

Figure 1 Flow chat of participants selection. Figure indicated that total of 5023 residents were recruited in this cohort during the study periods. After exclusion the individuals who have the previous CVD (n=720) or stroke history (n=355), 3948 participants were analysed in this study finally.

Table 1 Baseline Characteristics of Study Participants

Characteristics	Male	Female	Total
Cases, n (%)	1762 (44.6)	2186 (55.4)	3948
Age, year, mean (SD)	61.34 (10.10)	59.37 (9.54)	60.25 (9.84)
Age group, n (%)			
45–54 years	462 (26.2)	770 (35.2)	1232 (31.2)
55–64 years	709 (40.2)	873 (39.9)	1582 (40.1)
65–74 years	432 (24.5)	411 (18.8)	843 (21.4)
≥75 years	159 (9.0)	132 (6.0)	291 (7.4)
Education, means (SD), years	6.44 (3.00)	4.74 (3.70)	5.49 (3.51)
Education level, n (%)			
0 year	238 (13.5)	645 (29.5)	883 (22.4)
1–6 years	723 (41.0)	880 (37.0)	1531 (38.8)
>6 years	801 (45.5)	733 (33.5)	1534 (38.9)
Smoking, n (%)			
Never smoking	387 (22.0)	2064 (94.4)	2451 (62.1)
Ex-smoker	448 (25.4)	69 (3.2)	517 (13.1)
Current smoker	927 (52.6)	53 (2.4)	980 (24.8)
Drinking, n (%)			
Never drinking	549 (31.2)	2103 (96.2)	2652 (67.2)
Ex-drinker	269 (15.3)	41 (1.9)	310 (7.9)
Current drinker	944 (53.6)	42 (1.9)	986 (25.0)
BMI, means (SD), kg/m^2	24.93 (3.61)	25.85 (8.38)	25.44 (6.70)
BMI group, n (%)			
Low weight and Normal	723 (41.0)	722 (33.0)	1445 (36.6)
Over weight	713 (40.5)	939 (43.0)	1652 (41.8)
Obesity	326 (18.5)	525 (24.0)	851 (21.6)
Hypertension n (%)			
No	626 (35.5)	667 (30.5)	1293 (32.8)
Yes	1136 (64.5)	1519 (69.5)	2655 (67.2)
Diabetes n (%)			
No	1530 (86.8)	1821 (83.3)	3351 (84.9)
Yes	232 (13.2)	365 (16.7)	597 (15.1)
SBP, means (SD), mmHg	148.83 (21.03)	147.70 (28.07)	148.16 (25.45)
DBP, means (SD), mmHg	87.51 (10.65)	83.05 (10.72)	84.86 (10.91)
FBG, means (SD), mmol/L	5.68 (1.85)	5.63 (1.85)	5.66 (1.68)
TC, means (SD), mmol/L	4.79 (0.94)	5.14 (2.13)	4.98 (1.71)
TG, means (SD), mmol/L	1.57 (2.35)	1.68 (1.46)	1.63 (1.91)
HDL-C, means (SD), mmol/L	1.40 (0.54)	1.42 (0.40)	1.41 (0.47)
LDL-C, means (SD), mmol/L	2.74 (0.77)	2.95 (0.97)	2.86 (0.89)
Inflammatory indices, means (SD)			
NLR	2.01 (2.03)	1.73 (0.84)	1.86 (1.50)
MLR	0.23 (0.10)	0.20 (0.08)	0.21 (0.09)

Associations of NLR and MLR with the Risk of Stroke and All-Cause Death

The findings from univariate and multivariate Cox proportional hazards regression analyses of lymphocyte-based inflammatory indices for predicting stroke incidence and all-cause mortality are presented in Table 2.

Univariate analysis indicated that elevated NLR was significantly associated with an increased risk of stroke (HR: 1.965, 95% CI: 1.392–2.772, $P < 0.001$) and all-cause mortality (HR: 1.882, 95% CI: 1.405–2.521, $P<0.001$). Similarly, higher MLR levels correlated with an elevated risk of all-cause mortality (HR: 1.923, 95% CI: 1.480–2.497, $P <0.001$) and stroke (HR: 1.396, 95% CI: 1.088–1.792, $P = 0.009$).

Table 2 Cox Regression Analysis of the Associations Between NLR/MLR and Risks of Stroke and All-Cause Mortality

Outcomes	N (%)	HR (95% CI)		
		Model 1	Model 2	Model 3
NLR:				
All-cause death				
NLR<1.494	63 (4.1)	1 (reference)	1 (reference)	1 (reference)
NLR≥1.494	164 (6.8)	1.882 (1.405, 2.521)	1.604 (1.187, 2.167)	1.558 (1.148, 2.116)
P value		<0.001	0.002	0.004
Stroke				
NLR<1.266	38 (4.1)	1 (reference)	1 (reference)	1 (reference)
NLR≥1.266	224 (7.4)	1.965 (1.392, 2.772)	1.779 (1.252, 2.526)	1.776 (1.250, 2.254)
P value		<0.001	0.001	0.001
MLR:				
All-cause death				
MLR<0.233	120 (4.4)	1 (reference)	1 (reference)	1 (reference)
MLR≥0.233	107 (9.0)	1.923 (1.480, 2.497)	1.343 (1.020, 1.769)	1.397 (1.054, 1.852)
P value		<0.001	0.036	0.020
Stroke				
MLR<0.197	101 (5.2)	1 (reference)	1 (reference)	1 (reference)
MLR≥0.197	161 (8.1)	1.396 (1.088, 1.792)	1.150 (0.885, 1.496)	1.166 (0.897, 1.515)
P value		0.009	0.296	0.252

Notes: Model 1: Unadjusted analysis. Model 2: Adjusted for age, sex, education level, smoking status, alcohol consumption, and body mass index (BMI). Model 3: Further adjusted for the variables included in Model 2, along with hypertension, diabetes, total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C).

In multivariate analysis (Model 3), adjusting for potential confounders such as age, sex, education, smoking status, alcohol use, BMI, hypertension, diabetes, TC, and LDL-C, a higher NLR remained a significant predictor of stroke risk (HR: 1.776, 95% CI: 1.250–2.254, *P* = 0.001) and all-cause mortality (HR: 1.558, 95% CI: 1.148–2.116, *P* = 0.004). Elevated MLR was associated with all-cause mortality (HR: 1.397, 95% CI: 1.054–1.852, *P* = 0.020), but not with stroke incidence (HR: 1.166, 95% CI: 0.897–1.515, *P* = 0.252).

Evaluation of the Prognostic Performance of the NLR and MLR for Stroke and All-Cause Mortality

ROC curve analysis was performed to assess the predictive power of NLR/MLR for stroke and all-cause mortality. The results indicated that the predictive performance of NLR (AUC: 0.55, 95% CI: 0.52–0.59, *P* = 0.005) and MLR (AUC: 0.58, 95% CI: 0.54–0.62, *P* < 0.001) for stroke was comparable (Figure 2A). Similarly, no significant difference was observed in the predictive ability of NLR (AUC: 0.57, 95% CI: 0.53–0.61, *P* < 0.001) and MLR (AUC: 0.61, 95% CI: 0.57–0.65, *P* < 0.001) for all-cause mortality (Figure 2B). These results demonstrated that both NLR and MLR relatively low predictive value for stroke and all-cause mortality. The optimal thresholds for predicting disease risk were identified using the Youden Index, with critical cutoff values of 1.266 NLR and 0.197 MLR for stroke incidence; and the cutoff values were 1.494 NLR and 0.233 MLR for all-cause mortality. The results in Table 3 show that for stroke prediction, the MLR model has a slightly higher AUC (0.58) compared to the NLR model (0.55), indicating a modest predictive advantage. In predicting all-cause mortality, the MLR model again outperforms the NLR model with an AUC of 0.61 versus 0.57. The MLR model also demonstrates better specificity in mortality prediction (0.71) compared to stroke prediction (0.50), along with a strong negative predictive value of 0.96 for mortality. These findings suggest that the MLR model provides a marginally more accurate prediction across the assessed outcomes.
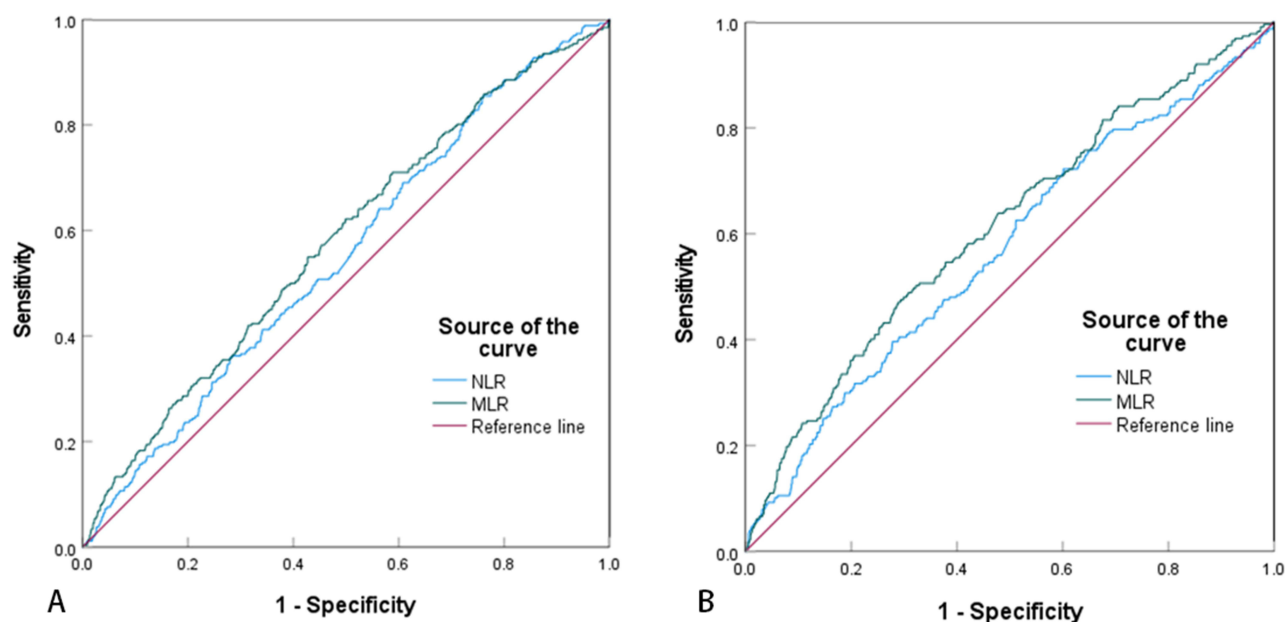
Figure 2 Evaluation of the prognostic performance of the NLR and MLR for stroke and all-cause mortality. Figure indicated that the predictive performance of NLR (AUC: 0.55, 95% CI: 0.52–0.59, P = 0.005) and MLR (AUC: 0.58, 95% CI: 0.54–0.62, P < 0.001) for stroke was comparable (**A**). Similarly, no significant difference was observed in the predictive ability of NLR (AUC: 0.57, 95% CI: 0.53–0.61, P < 0.001) and MLR (AUC: 0.61, 95% CI: 0.57–0.65, P < 0.001) for all-cause mortality (**B**).

Discussion

This prospective cohort study, conducted in a low-income rural population in China, explored the associations of the NLR and MLR with stroke and all-cause mortality. We found that elevated levels of both NLR and MLR were independently associated with an increased risk of all-cause mortality. Notably, NLR was also identified as a significant predictor of stroke incidence, while MLR did not show a statistically significant association with stroke. We also studied the association between NLR/MLR and all-cause mortality and their predictive role in this population.

Table 3 Performance Indicators for MLR and NLR in Stroke and Mortality Prediction

Indicator/Variable	Stroke Prediction (NLR)	Stroke Prediction (MLR)	All-Cause Mortality Prediction (NLR)	All-Cause Mortality Prediction (MLR)
AUC	0.55	0.58	0.57	0.61
95% CI	0.52–0.59	0.54–0.62	0.53–0.61	0.57–0.65
P-value	0.005	<0.001	<0.001	<0.001
Optimal Cutoff	1.266	0.197	1.494	0.233
Youden Index	0.09	0.11	0.12	0.18
Sensitivity	0.85	0.61	0.72	0.47
Specificity	0.24	0.50	0.40	0.71
Positive Predictive Value (PPV)	0.07	0.08	0.07	0.09
Negative Predictive Value (NPV)	0.96	0.95	0.96	0.96
Positive Likelihood Ratio (PLR)	1.12	1.22	1.20	1.62
Negative Likelihood Ratio (NLR)	0.63	0.78	0.70	0.75
Diagnostic Odds Ratio (DOR)	1.78	1.56	1.71	2.16

Note: P-value, statistical significance with P < 0.05 considered significant.
Abbreviations: AUC, Area Under the Curve; CI, Confidence Interval; PPV, Positive Predictive Value; NPV, Negative Predictive Value; PLR, Positive Likelihood Ratio; NLR, Negative Likelihood Ratio; DOR, Diagnostic Odds Ratio.

These findings highlight the potential of these inflammatory indices as practical biomarkers for predicting health outcomes in underserved populations. Our study adds to the growing body of literature examining the role of inflammatory markers in vascular disease and mortality, particularly in low-income populations.[18]

Chronic inflammation is a well-known risk factor in the pathogenesis of vascular disease as well as including infectious diseases, tumors, and both NLR and MLR have been established as valuable markers in general populations.[19–21] Inflammation is widely recognized as a critical factor in the development of cardiovascular diseases.[22–24] Several studies highlight the role of novel inflammatory indices in cardiovascular diseases. For example, Ridker PM et al reported that inflammation as a predictor of cardiovascular events in patients undergoing statin therapy[25] and also showed that the NLR can assess ziltivekimab's clinical effectiveness.[26] NLR, a biomarker for inflammation and oxidative stress in cardiovascular diseases, is associated with all-cause mortality, coronary heart disease, and heart failure.[27,28] It is a strong independent risk factor for mortality, especially in the elderly, and correlates with the prognosis of coronary artery disease, including acute coronary syndrome.[29–31] Growing evidence has demonstrated that neutrophils and monocytes are central players in these processes. Elevated neutrophil levels, indicative of an inflammatory state, have been linked to adverse outcomes in cardiovascular diseases and cerebrovascular, while monocytes contribute to the progression of atherosclerotic plaques and vascular instability.[32,33]

Studies on the predictive mechanisms of inflammatory indicators has mostly focused on cardiovascular diseases. Leukocytes, essential for immune defense, release cytokines and chemokines (eg, interleukins and TNF) that activate innate immune pathways like the inflammasome.[34] Monocytes, neutrophils, and lymphocytes are key players in cardiovascular disease.[35] Neutrophils contribute to inflammation by releasing mediators, chemotactic factors, and reactive oxygen species, which damage the endothelium and promote atherosclerosis.[36] Monocytes, which circulate in the blood and respond to inflammatory signals, migrate into blood vessel walls, differentiate into macrophages, and play a critical role in cardiovascular disease progression.[37] These macrophages, through phagocytosis and inflammatory responses, drive the development and instability of atherosclerotic plaques.[38] Studies have also shown that inflammation accelerates atherosclerosis and the development of stroke through mechanisms such as endothelial damage, oxidative stress, and plaque instability because cardiovascular and cerebrovascular diseases share similar pathogenic mechanisms.[27] Recent studies on inflammatory markers associated with stroke have identified several promising candidates for predicting early neurological recovery and stroke outcomes. For instance, neutrophil-to-lymphocyte ratios have been linked to improved neurological function post-thrombolysis. Some studies also highlight the importance of pre-thrombolysis leukocyte counts and blood pressure changes in predicting recovery. These biomarkers offer potential for stratifying stroke patients for better therapeutic interventions.[39–42] Additionally, Huang et al found that an elevated MLR increases stroke risk.[43] Li et al demonstrated that NLR is an important risk factor for all-cause mortality and cardiovascular mortality in patients with cardiovascular disease.[14] Wang et al showed that NLR is a significant indicator for assessing the risk of death in individuals with metabolic syndrome.[15] Zhu et al discovered that NLR and MLR have clinical value in predicting short-term outcomes in patients with acute ischemic stroke.[16] Our study similarly indicates that NLR is associated with an increased risk of stroke incidence and all-cause mortality. However, our findings suggest that MLR is only related to all-cause mortality, with no significant association observed between MLR and stroke risk, this is different from the conclusions of previous studies that have shown an association between MLR and stroke incidence. These differences may be attributed to variations in sample size, study design, and the distinct characteristics of the study populations. This study focuses on the rural low-income population, whereas previous studies have lacked attention to this particular group. Although studies have examined the associations of MLR and NLR with cardiovascular diseases as well as stroke, studies reporting these relationships in low-income populations are lacking. Our study offers foundational evidence for the early prevention of stroke in this specific population. Additionally, we confirm the association between NLR/MLR and all-cause mortality, consistent with findings in other populations.

In this study, we also conducted a ROC curve analysis to assess the predictive performance of NLR and MLR for stroke and all-cause mortality. Although NLR and MLR were significantly associated with mortality and NLR was significantly associated with stroke incidence, the prediction was not ideal. However, these findings provide evidence for the potential clinical utility of NLR and MLR as available, cost-effective tools for identifying individuals at high risk for cerebrovascular events, particularly in resource-limited environments, which still need to be further validated.

This study contributes to the literature by providing the first prospective cohort evidence from a low-income rural population demonstrating that NLR is independently associated with both stroke risk and all-cause mortality, while MLR is associated with all-cause mortality. Unlike previous studies that primarily focused on high-income or general populations, our study provides valuable insights into how these readily available inflammatory markers may assist in early risk stratification in resource-constrained settings. Our findings suggest that while NLR and MLR have a modest predictive capacity, their accessibility and low cost make them potentially useful in supplementing existing risk assessment strategies, particularly in populations with limited access to advanced diagnostic tools. By addressing these research gaps, our study highlights the necessity of further investigations to validate these associations in larger, more diverse cohorts and to explore their integration into predictive models that combine traditional and novel risk factors. This work lays a foundation for future studies aimed at refining stroke and mortality risk prediction, ultimately contributing to more effective and personalized preventive strategies for cerebrovascular diseases.

The strengths of our study include a large sample size and the inclusion of a unique rural, low-income population, offering critical evidence for the utility of inflammatory markers in populations with limited access to medical resources. This is particularly significant as cerebrovascular diseases, such as stroke and cardiovascular disease, are increasingly prevalent in low-income populations, who often face substantial barriers to accessing healthcare. The longitudinal design of the study, with a mean follow-up of 7 years, enabled the evaluation of time-dependent associations between inflammatory markers and long-term health outcomes, enhancing the study's rigor and the reliability of its findings.

Limitations

Several limitations in this study must be acknowledged. First, the reliance on self-reported medical histories introduces the potential for information bias. Second, while our study focused on stroke and all-cause mortality, we did not evaluate other important cardiac events, such as heart failure, which are also relevant outcomes in this population. Additionally, our study utilized only a single baseline measurement of white blood cell counts (WBC). This approach may not fully capture the dynamic nature of inflammation over time, the variability in white blood cell counts may impact the reliability of single measurements, suggesting that future research would benefit from repeated assessments over time to better capture temporal fluctuations in inflammatory markers. Moreover, the ROC analysis revealed relatively low AUC values, indicating limited predictive performance of the current model. Finally, while our findings provide a framework for predicting stroke and all-cause mortality in low-income rural populations, further studies are necessary to assess the generalizability of these biomarkers in other underserved communities or populations with differing demographics.

Future Directions

Future research should address the limitations identified in this study. Specifically, validating our findings in other low-income populations or those with different demographic characteristics would enhance the generalizability of our results. Additionally, incorporating repeated measurements of inflammatory markers over time could provide a more accurate assessment of their predictive value. Given the potential for information bias from self-reported data, future studies might consider using electronic health records or other objective sources of medical history to improve data accuracy. Furthermore, exploring the associations between NLR/MLR and other cardiovascular outcomes, such as heart failure, would provide a more comprehensive understanding of their role in vascular disease. Moreover, future research should aim to improve the predictive performance of the model by incorporating additional biomarkers or optimizing statistical methods to enhance the AUC values of ROC curves. Finally, investigating the potential mechanisms underlying the associations between these inflammatory indices and cerebrovascular events could offer new insights into the pathophysiology of stroke and inform targeted preventive interventions.

Conclusion

This prospective cohort study highlights the significant associations between neutrophil-to-lymphocyte ratio (NLR) and both stroke incidence and all-cause mortality, as well as between monocyte-to-lymphocyte ratio (MLR) and all-cause mortality in a low-income rural population. Given that these inflammatory markers are readily available and cost-effective, they may serve as practical tools for early risk identification and stratification, particularly in resource-limited settings where access to advanced diagnostic methods is restricted. Despite demonstrating statistically significant associations, the predictive ability of NLR and MLR remains modest, as reflected in the AUC values. Therefore, while these markers may complement traditional risk assessment models, they should not be used in isolation for clinical decision-making. Instead, incorporating NLR and MLR into routine health assessments alongside conventional cardiovascular risk factors may enhance personalized risk stratification, facilitate targeted preventive strategies, and optimize healthcare resource allocation in underserved populations. From a clinical perspective, the integration of NLR and MLR into routine screening programs could help identify high-risk individuals for stroke and mortality, allowing for timely interventions such as lifestyle modifications, regular monitoring, and targeted medical management. However, further studies are necessary to refine their application in clinical practice. To strengthen the evidence base, future research should focus on validating these findings in larger and more diverse populations to assess their generalizability. Additionally, investigating the integration of NLR and MLR with other inflammatory, metabolic, or genetic biomarkers may improve their predictive accuracy for stroke and mortality. Longitudinal and interventional studies are also warranted to determine whether modifying inflammatory status—through pharmacological treatments or lifestyle interventions—can alter NLR and MLR levels and subsequently improve patient outcomes. Furthermore, developing comprehensive predictive models that incorporate inflammatory markers, conventional cardiovascular risk factors, and imaging findings may enhance individualized risk stratification and stroke prevention strategies. By addressing these research gaps, future studies can enhance the clinical utility of NLR and MLR, bridge the gap between biomarker-based risk prediction and clinical decision-making, and ultimately contribute to the development of more effective and personalized strategies for stroke prevention, particularly in low-resource settings.

Abbreviations

NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; AUC-ROC, area under the receiver operating characteristic curve; GBD, Global Burden of Diseases; DALYs, disability-adjusted life-years; CRP, C-reactive protein; IL-6, interleukin 6; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CBC, complete blood count; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; SD, standard deviation; IQR, interquartile range; ROC, receiver operating characteristic; HRs, hazard ratios; Cis, confidence intervals.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

This study adhered to the principles of the Declaration of Helsinki and was approved by the Tianjin Medical University General Hospital Ethics Committee (Approval No. [IRB2018-099-01]). A written informed consent was obtained from all participants.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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