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Neutrophil/High-density lipoprotein Cholesterol ratio and Outcomes in patients with acute ischemic stroke.

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SUMMARY: *To determine whether the neutrophil-to-high-density lipoprotein cholesterol ratio (NHR) can predict the functional outcome of a first-episode acute ischemic stroke (AIS) after 90 days, a retrospective cohort study was carried out. Consecutive AIS patients admitted to Suining Central Hospital within 72 hours of symptom onset between August 2022 and August 2023 were screened, and 527 patients with complete clinical, laboratory, imaging and follow-up data were included. Functional outcome was assessed at 90 days after the modified Rankin Scale, and scores of 0-2 were considered a favourable outcome; scores of 3-6 were considered a poor outcome. NHR was calculated based on the admission neutrophil count and HDL-C, and then its prognostic value was investigated through quartile grouping, binary logistic regression, receiver operating characteristic (ROC) curve analysis and pre-specified subgroup analysis. A poor outcome occurred in 199 cases (37.8%). The optimal NHR cutoff was 4.724, and continuous NHR was still independently associated with poor 90-day outcomes after adjusting for age, sex, admission NIHSS score, stroke type, atrial fibrillation, coronary heart disease, neutrophil count, lymphocyte count and HDL-C (OR 2.19, 95% CI 1.50-3.18, $p < 0.001$). NHR achieved an AUC of 0.716 and was relatively high among the other composite inflammatory indices and close to NLR. Subgroup analysis showed a stronger association among males, patients older than 70 years, hypertensive patients, non-diabetic patients, and those with moderate- to severe baseline neurological deficits. Based on the above studies, NHR can be used as a relatively easy-to-obtain marker for short-term risk assessment after an AIS, but multi-center verification and mechanistic investigations are still needed.*

KEYWORDS: *acute ischemic stroke; neutrophil-to-HDL cholesterol ratio; modified Rankin Scale; inflammation; short-term prognosis*

1 Introduction

Acute ischaemic stroke (AIS) is the most frequent type of stroke, and many people are still dying or severely impaired due to this cause and requiring extended care. According to the 2021 Global Burden of Disease report, the number of people around the world with strokes continues to increase; therefore, early diagnosis, high-level grading, prompt imaging, control of vascular risk factors and goal-oriented rehabilitation are all necessary for timely treatment of acute ischaemic stroke (AIS) in individuals with acute ischaemic stroke. The modified Rankin Scale (mRS) at 90 days is commonly employed in routine clinical research to distinguish between independent or near-independent recovery and disability or death, and is thus suitable for short-

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term prognostic modeling in AIS cohorts [1-3].

Low-cost blood biomarkers are feasible because they can be obtained before high-end imaging analysis or in the long term. Peripheral inflammatory indicators such as neutrophil counts and the neutrophil-to-lymphocyte ratio (NLR) have been associated with the severity of stroke and functional impairment, but these single-cell-count indices do not consider lipid-linked vascular protection. Recently, AIS research has been conducted to build a composite inflammatory index by combining NHR, the systemic inflammatory response index, the systemic immune-inflammation index and platelet-related ratios, etc., in order to improve risk stratification beyond traditional clinical factors [4-8].

NHR combines two biologically opposed signals. Neutrophils are early in ischemic tissue; they release reactive oxygen species and matrix metalloproteinases to promote microvascular obstruction and exacerbate blood-brain barrier disruption. Increase reverse cholesterol transport via HDL-C, reduce endothelial inflammation and leukocyte activation, and demonstrate anti-oxidant and anti-thrombotic functions. Therefore, a relatively high NHR suggests that inflammatory injury is more pronounced than lipid-mediated vascular protection. Research on cardiovascular disease and stroke-related complications has connected NHR with coronary stenosis, acute myocardial infarction, hemorrhagic transformation and outcomes after thrombolysis, but evidence in unselected first-episode AIS patients is still lacking [9-23].

Assess whether admission to the North Highland Hospital (NHR) is related to functional outcomes 90 days after the first episode of amyotrophic lateral sclerosis (ALS) for patients, evaluate the discriminative power of this index in comparison to other inflammatory indexes, and study whether the association changes in different groups with different clinical characteristics. The study uses a measurable index, has a specific follow-up indicator, and an open-ended adjustment system instead of a general inflammation theory.

2 Materials and Methods

2.1 Study Design and Patient Selection

This hospital-based retrospective cohort study included consecutive patients with a first-episode AIS admitted to the Department of Cerebrovascular Disease at Suining Central Hospital from August 2022 to August 2023. Based on the diagnosis of AIS, there were clinical features of cerebral ischemia, and CT or MRI had to be performed within 72 hours of symptom onset for confirmation. The inclusion criteria were: first-episode AIS, admission within 3 days of the onset of symptoms, available admission laboratory tests, and completed 90-day outcome assessment. Pre-stroke modified Rankin Scale (mRS) ≥ 2, transient ischaemic attack (TIA), severe infection, major trauma or surgery, immunosuppressive or glucocorticoid therapy in the past 6 months, thrombolytic therapy, major cardiovascular, hepatic, renal, hematological, immunologic or malignant diseases, antiplatelet or statin exposure within the 60 days before admission, incomplete records, or failure to complete follow-up.

The Screening Process is as follows: Figure 1. Of the 802 screened records, 218 were excluded based on the set standards; 584 met the requirements and 57 were lost to follow-up. The final analytic cohort had 527 patients, and among them, 199 had poor 90-day outcomes.

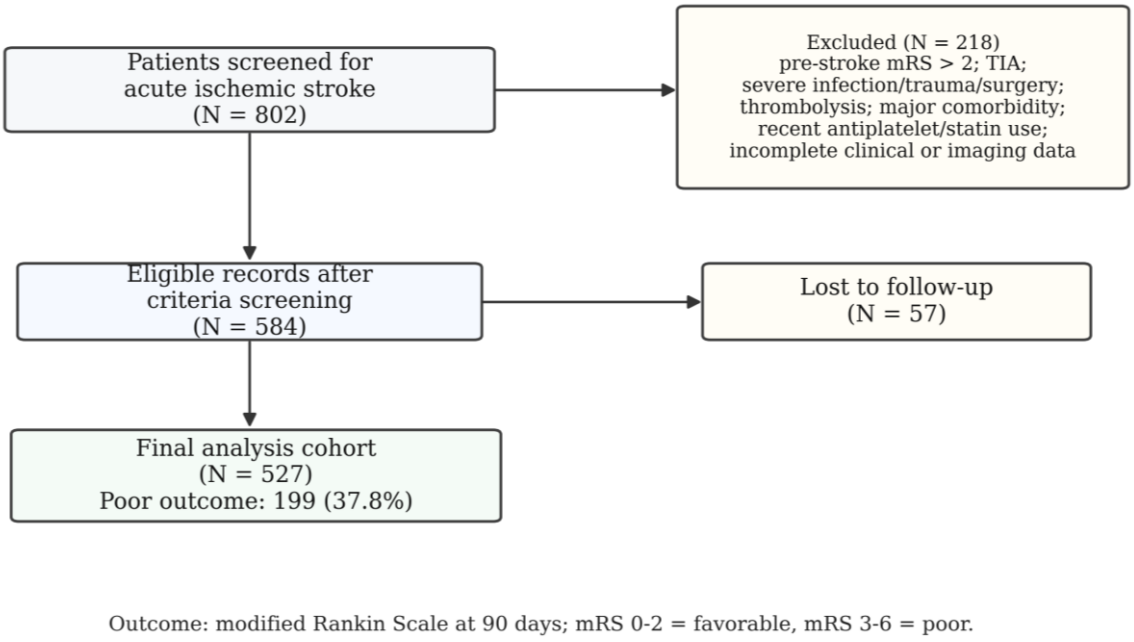

Figure 1: Patient Selection and Final Analytic Cohort Construction for AIS Prognosis Analysis.

Figure 1 is the denominator of the statistical analysis. The exclusion stage primarily excluded patients whose inflammatory or lipid levels would be altered by pre-stroke disability, acute infection, recent interventions, major comorbidities, thrombolytic therapy, or incomplete data. The final outcome distribution showed that among the 527 patients, 199 had poor outcomes and thus provided a sufficient event proportion of 37.8% for multivariable modelling with the pre-specified covariates.

2.2 Clinical Variables and Laboratory Measurements

Demographic Information: Age and Sex. The causes of the clinical history were: high blood pressure, diabetes, atrial fibrillation, coronary heart disease, smoking and alcohol consumption. Systolic and diastolic Blood Pressure were taken at the start. The level of the stroke was determined by the National Institutes of Health Stroke Scale (NIHSS): mild (1-4), moderate (5-15), or severe ($\geq$16). Stroke cause was classified as large-artery atherosclerosis, small-vessel atherosclerosis, cardioembolism, stroke due to other determined reasons, or stroke of unknown causes. Hypertension was defined as a history of previous antihypertensive medication use, systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg. Diabetes mellitus was defined as having a history of hypoglycaemic treatment, fasting glucose $\geq$7.0mmol/L, or postprandial glucose $\geq$11.1mmol/L.

Fasting venous blood samples were taken in the morning after hospitalisation. Neutrophils, lymphocytes, platelets and monocytes were also counted in a complete blood count on a Sysmex XN-1000 hematology analyzer. A Beckman Coulter AU5800 biochemical analyzer was used to measure the concentrations of triglycerides, total cholesterol, low-density lipoprotein cholesterol, HDL-C, albumin, uric acid, C-reactive protein and fibrinogen. NHR was taken from the first available fasting blood work to avoid changes after treatment.

2.3 Formula Construction and Outcome Definition

The first exposure variable NHR is as follows:

$$\mathrm{NHR}_i = \frac{\mathrm{NE}_i}{\mathrm{HDL-C}_i} \tag{1}$$

NE_i and $\mathrm{HDL-C}_i$ are the admission neutrophil count and high-density lipoprotein cholesterol concentration of patient i, respectively.

The comparison indices of inflammation used in ROC analysis were set as follows:

$$\mathbf{R}_i = \left\{\frac{\mathrm{FIB}_i}{\mathrm{ALB}_i}, \frac{\mathrm{CRP}_i}{\mathrm{ALB}_i}, \frac{\mathrm{PLT}_i}{\mathrm{Lym}_i}, \frac{\mathrm{Lym}_i}{\mathrm{MONO}_i}, \frac{\mathrm{NE}_i}{\mathrm{PLT}_i}, \frac{\mathrm{PLT}_i}{\mathrm{ALB}_i}, \frac{\mathrm{CRP}_i}{\mathrm{Lym}_i}, \frac{\mathrm{MONO}_i}{\mathrm{HDL-C}_i}, \frac{\mathrm{NE}_i}{\mathrm{Lym}_i}\right\} \tag{2}$$

Corresponding to FAR, CAR, PLR, LMR, NPR, PAR, CLR, MHR and NLR.

The 90-day outcome variable selected is:

$$Y_i = \begin{cases} 1, \mathrm{mRS}_i \geq 3, \\ 0, \mathrm{mRS}_i \leq 2. \end{cases} \tag{3}$$

A value of Y_i = 1 indicated a poor functional outcome, such as moderate-to-severe disability or death; otherwise, Y_i = 0.

2.4 Statistical Modeling

Test the distribution of continuous variables and present the mean ± standard deviation or median (interquartile range). The Frequency and Proportion of Categories were reported. Appropriate comparisons of the above groups were conducted using T-tests, analysis of variance (ANOVA), Mann-Whitney U tests, Kruskal-Wallis tests, chi-square tests and Fisher's exact tests. NHR was checked continuously and also as quartiles. Many logistic regressions were employed to investigate the effect of NHR on poor 90-day outcomes after adjusting for variables with clinical significance and those selected by univariate screening.

The modified logistic model is as follows:

$$\begin{aligned}\mathrm{logit}[P(Y_i = 1)] = \beta_0 + \beta_1 \mathrm{NHR}_i + \beta_2 \mathrm{Age}_i + \beta_3 \mathrm{Sex}_i + \beta_4 \mathrm{NIHSS}_i + \beta_5 \mathrm{Etiology}_i + \beta_6 \mathrm{AF}_i + \\ \beta_7 \mathrm{CHD}_i + \beta_8 \mathrm{NE}_i + \beta_9 \mathrm{Lym}_i + \beta_{10} \mathrm{HDL-C}_i\end{aligned} \tag{4}$$

AF is atrial fibrillation and CHD is coronary heart disease. ROC analysis was performed to obtain the AUC value and sensitivity-specificity trade-off points. The optimal threshold was selected based on the Youden's index: J = sensitivity + specificity - 1. A Delong's Test is used to compare the AUCs of NHR and the other composite indices. The report logic met the requirements for a transparent multi-variable prediction report by setting end points, listing covariates and presenting clinically interpretable effect sizes [24-26].

2.5 Ethics

The Ethics Committee of Suining Central Hospital has approved the study plan (KYLLKS20240011). Waived informed consent in accordance with the relevant national and institutional regulations for retrospective analysis of de-identified clinical data.

3 Results

3.1 Baseline Characteristics by NHR Quartile

The final cohort had a mean age of 70.03 ± 11.25 years and contained 214 female patients (40.6%), with a total of 527 AIS patients. Before performing outcome modeling, the baseline

values of the NHR quartiles were compared to determine whether higher NHR was due to increased lipid levels or other reasons in an inflammatory state. Table 1 shows the quartile-stratified baseline data.

Table 1: Demographic and Clinical Characteristics by NHR Quartiles.

Variable	Total (n=527)	Q1 (n=130)	Q2 (n=135)	Q3 (n=130)	Q4 (n=132)	P value
NHR	10.03±11.24	2.25±0.49	3.55±0.37	4.88±0.54	8.05±2.10	<0.001
Age (years)	70.03±11.25	70.29±10.32	69.16±11.39	69.28±10.92	71.33±12.24	0.354
Female, n (%)	214(40.6%)	53(10.1%)	51(9.7%)	51(9.7%)	59(11.2%)	0.690
Hypertension, n (%)	368(69.8%)	87(16.5%)	83(15.7%)	102(19.4%)	96(18.2%)	0.180
Diabetes, n (%)	186(35.3%)	39(7.4%)	47(8.9%)	50(9.5%)	50(9.5%)	0.463
Atrial fibrillation, n (%)	71(13.5%)	13(2.5%)	16(3.0%)	16(3.0%)	26(4.9%)	0.103
CHD,n (%)	30(5.7%)	9(1.7%)	8(1.5%)	4(0.8%)	9(1.7%)	0.503
Smoker, n (%)	115(21.8%)	33(6.3%)	28(5.3%)	30(5.7%)	24(4.6%)	0.531
Alcohol user, n (%)	87(16.5%)	20(3.8%)	25(4.7%)	29(5.5%)	13(2.5%)	0.047
Etiological subtype,n (%)						<0.001
LAA	214(40.6%)	45(8.5%)	35(6.6%)	54(10.2%)	80(15.2%)	
SAA	227(43.1%)	73(13.9%)	75(14.2%)	57(10.8%)	22(4.2%)	
CE	68(12.9%)	12(2.3%)	14(2.7%)	16(3.0%)	26(4.9%)	
SOE+SUE	18(3.4%)	0(0.0%)	11(2.1%)	3(0.6%)	4(0.8%)	
NIHSS						<0.001
mild (1≤NIHSS≤4)	287(54.5%)	93(17.6%)	83(15.7%)	73(13.9%)	38(7.2%)	
moderate (5≤NIHSS≤15)	202(38.3%)	35(6.6%)	45(8.5%)	52(9.9%)	70(13.3%)	
severe (16≤NIHSS score)	38(7.2%)	2(0.04%)	7(1.3%)	5(0.9%)	24(4.6%)	
Lym (109/L)	1.51±0.71	1.48±0.61	1.59±0.70	1.53±0.71	1.44±0.77	0.341
NE (109/L)	5.94±2.69	3.59±0.99	4.83±0.99	6.46±1.78	8.88±2.88	<0.001
ALB (g/l)	40.42±4.43	40.37±4.51	41.06±3.81	40.82±4.93	39.44±4.31	0.016
HDL (mmol/L)	1.37±0.62	1.69±1.08	1.36±0.27	1.32±0.33	1.12±0.29	<0.001
LDL (mmol/L)	3.12±0.92	2.99±0.92	3.19±0.88	3.10±0.89	3.18±0.98	0.251
TC (mmol/L)	5.12±1.22	5.10±1.16	5.17±1.18	5.12±1.18	5.10±1.35	0.952
TG (mmol/L)	2.05±2.40	1.62±1.25	2.11±1.61	2.04±1.76	2.41±3.95	0.067
UA (umol/L)	337.96±107.451	321±107.59	69.16±11.39	69.28±10.92	71.33±12.24	0.080
CRP (mg/L)	1.85(0.50,5.36)	1.13(0.50,2.79)	1.48(0.50,4.24)	1.97(0.50,5.01)	4.13(1.27,11.31)	<0.001
FIB(g/L)	3.34±1.13	3.14±0.88	3.22±0.74	3.38±1.12	3.61±1.55	0.003
PLT (109/L)	196.87±69.17	188.06±67.92	192.22±62.77	204.20±67.98	203.06±76.77	0.544
MONO (109/L)	0.53±0.24	0.46±0.17	0.51±0.21	0.54±0.25	0.62±0.28	0.068
Unfavorable outcome, n (%)	199(37.8%)	25(4.7%)	38(7.2%)	46(8.7%)	90(17.1%)	<0.001

*NHR quartiles: Q1 (<=2.25), Q2 (2.26-3.55), Q3 (3.56-4.88), and Q4 (>=4.89). Abbreviations: LAA, large-artery atherosclerosis; CE, cardioembolism; SAA, small-vessel atherosclerosis; SOE, stroke of other etiology; SUE, stroke of undetermined etiology; NIHSS, National Institutes of Health Stroke Scale; Lym, lymphocyte; NE, neutrophil; ALB, albumin; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; UA, uric acid; CRP, C-reactive protein; FIB, fibrinogen; PLT, platelet; MONO, monocyte.

As shown in Table 1, neutrophil counts increased progressively with higher quartiles of NHR, rising from 3.59 ± 0.99 in Q1 to 8.88 ± 2.88 in Q4; simultaneously, HDL-C decreased from 1.69 ± 1.08 mmol/L to 1.12 ± 0.29 mmol/L. Therefore, the NHR pattern indicates that both inflammatory elevation and a decrease in HDL-C occurred simultaneously; only one was abnormal. The highest NHR quartile also included more large-artery atherosclerotic stroke cases, had a higher CRP, a higher fibrinogen, and a larger proportion of unfavorable outcomes; thus, NHR aligned with both a vascular cause and inflammation.

3.2 Baseline Characteristics by 90-Day Functional Outcome

Patients were then divided according to the 90-day modified Rankin Scale (mRS), and differences in various factors between the good-prognosis and poor-prognosis groups were analysed multivariably. Table 2 is the result-stratified comparison.

Table 2: Baseline Characteristics Stratified by 90-Day Functional Outcome.

Variable	Good outcome (n = 328)	Poor outcome (n = 199)	P value
Age (years)	70±16	72.96±10.57	<0.001
Female, n (%)	114 (34.8)	100 (50.3)	<0.001
Hypertension, n (%)	231 (62.8)	137(37.2)	0.701
Diabetes, n (%)	116 (62.4)	70(37.6)	0.965
Atrial fibrillation, n (%)	33 (46.5)	38 (53.5)	0.004
CHD,n (%)	13 (43.3)	17 (56.7)	0.032
Smoker, n (%)	77(67.0)	38 (33.0)	0.239
Alcohol user, n (%)	61(70.1)	26(29.9)	0.099
Etiological subtype,n (%)			<0.001
LAA	126(38.4)	88(44.2)	
SAA	165(50.3)	62(31.2)	
CE	27(8.2)	41(20.6)	
SOE+SUE	10(3.0)	8(4.0)	
NIHSS			<0.001
mild(1≤NIHSS≤4)	253(48.0%)	34(6.5%)	
moderate(5≤NIHSS≤15)	72(13.7%)	130(24.7%)	
severe(16≤NIHSS score)	3(0.6%)	35(6.6%)	
Lym (g/l)	1.46±0.85	1.29±0.92	<0.001
NE (g/l)	4.77±2.38	6.96±3.58	<0.001
ALB (g/l)	40.58±4.60	40.19±4.14	0.306
HDL (mmol/l)	1.34±0.49	1.26±0.43	<0.001
LDL (mmol/l)	3.00±1.97	3.19±1.37	0.059
TC (mmol/l)	5.00±1.47	5.19±1.76	0.160
TG (mmol/l)	1.57±1.13	1.34±1.03	0.735
UA (mmol/l)	340.38±100.31	333.96±118.44	0.506
CRP (mg/l)	5.89±13.67	7.57±12.33	0.162
FIB (g/l)	3.29±0.98	3.42±1.34	0.210
PLT (g/l)	197.32±67.21	196.12±72.44	0.846
MONO (g/l)	0.53±0.24	0.53±0.24	0.933
NHR	3.72±2.05	5.53±3.77	<0.001

Table 2 shows that poor outcomes are associated with older age, female sex, atrial fibrillation, coronary heart disease, etiological subtype, a higher admission NIHSS category, a

higher neutrophil count, a lower lymphocyte count, lower HDL-C, and a higher NHR. Clinically speaking, the results were different: Only 34 of the 287 patients in the mild NIHSS group had a poor outcome, and only 35 of the 38 patients in the severe NIHSS group had a poor outcome. NHR was also significantly higher in the group with a poor outcome (5.53 ± 3.77) than in the group with a good outcome (3.72 ± 2.05), and thus was included in the adjusted regression analysis.

3.3 Association between NHR and Poor 90-Day Outcome

Univariate analyses identified the following factors associated with the 90-day outcome: age, sex, admission NIHSS score, stroke etiology, atrial fibrillation, coronary heart disease, neutrophil count, lymphocyte count, HDL-C and NHR. Therefore, to determine if NHR still had a prognostic effect after controlling for stroke severity and other significant factors, it was added to the revised model. Regression results are as follows: Table 3.

Table 3: Univariate and Multivariate Regression Analysis of NHR and 90-Day Prognosis.

Outcomes	Crude				Adjusted*		
	OR (95% CI)	P value	P for trend		OR (95% CI)	P value	P for trend
Continuous variable	1.45(1.32-1.59)	<0.001			2.19 (1.50-3.18)	<0.001	
Quartile			<0.001				0.476
Q1 (n=130)	Reference				Reference		
Q2 (n=135)	1.65 (0.93-2.93)	0.09			1.35 (0.59-3.06)	0.480	
Q3 (n=130)	2.30 (1.31-4.05)	0.004			1.46 (0.55-3.91)	0.447	
Q4 (n=132)	9.00 (5.09-15.91)	<0.001			1.70 (0.38-7.61)	0.489	

Adjusted for age, sex, admission NIHSS score, stroke cause, history of atrial fibrillation, coronary heart disease, neutrophil count, lymphocyte count and HDL-C level.

Table 3 shows that NHR was strongly associated with an adverse outcome. After correction, NHR was still significantly associated with a continuous variable (OR 2.19, 95% CI 1.50-3.18, $p < 0.001$) in the model. The quartile model shows an increase in crude risk in Q3 and Q4; however, after adding NIHSS category, etiology, blood-cell/lipid components, etc., the adjusted quartile comparisons have been reduced. Therefore, the result of the continuous model is a more stable basis for the conclusion: higher admission NHR independently predicted poor 90-day functional outcomes, and quartile contrasts were sensitive to covariate adjustment.

3.4 ROC-Based Prognostic Performance

To determine whether NHR had practical discrimination and not just a statistical association, ROC analysis was performed with other composite inflammatory indices. Figure 2 is a ROC curve plot; Table 4 shows AUC values.

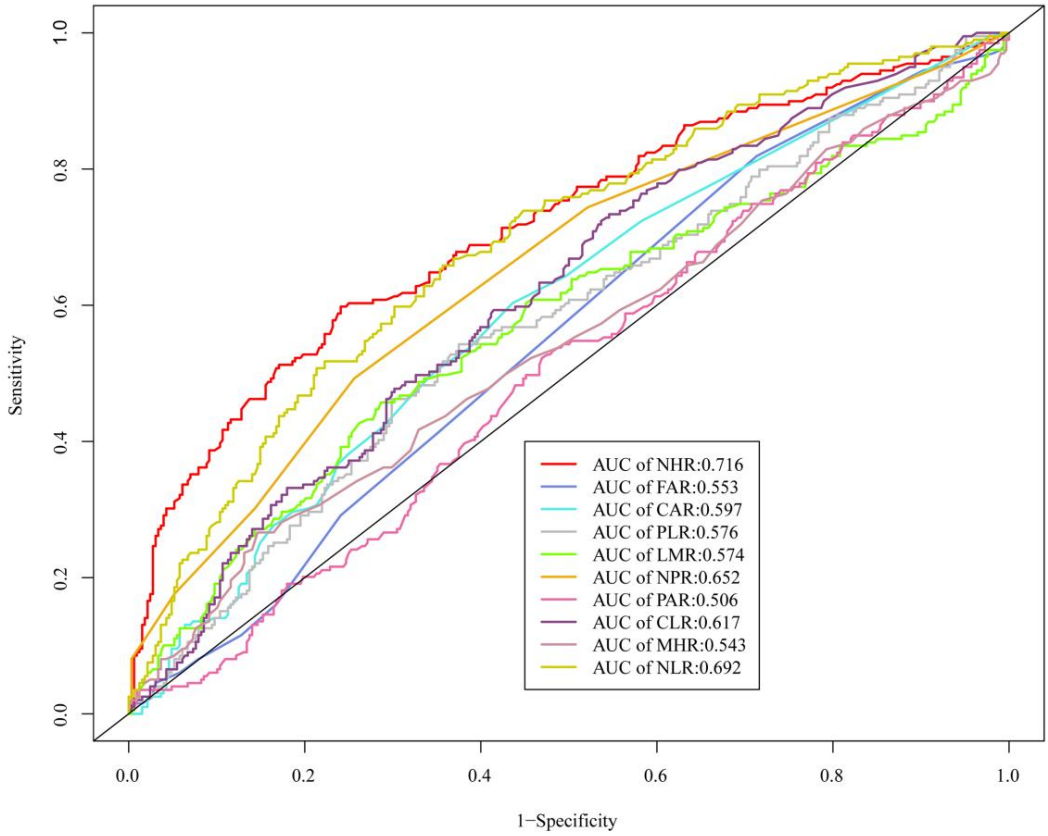

Figure 2: ROC Curves of NHR and Comparative Composite Inflammatory Indices in Predicting Poor 90-Day Outcome.

Table 4: Diagnostic Value of NHR and other Composite Inflammatory Indices for Unfavorable Outcome.

	AUC	P value
NHR	0.716	Reference
FAR	0.553	< 0.001
CAR	0.597	< 0.001
PLR	0.576	< 0.001
LMR	0.574	< 0.001
NPR	0.652	< 0.001
PAR	0.506	0.001
CLR	0.617	< 0.001
MHR	0.543	< 0.001
NLR	0.692	0.282

*NHR: neutrophil-to-HDL ratio; FAR: fibrinogen-albumin ratio; CAR: C-reactive protein-albumin ratio; PLR: platelet-lymphocyte ratio; LMR: lymphocyte-monocyte ratio; NPR: neutrophil-platelet ratio; PAR: platelet-albumin ratio; CLR: C-reactive protein-lymphocyte ratio; MHR: monocyte-HDL ratio; NLR: neutrophil-lymphocyte ratio.

Figure 2 and Table 4 show that NHR had an AUC of 0.716 and an optimal cutoff value of 4.724. Its AUC exceeded FAR, CAR, PLR, LMR, NPR, PAR, CLR and MHR, and the DeLong comparisons were statistically significant. NLR and NHR showed the same discriminatory power (AUC 0.692, p=0.282), and thus were considered equivalent neutrophil components. The

first addition of value for NHR is that it integrates neutrophil-mediated inflammation and HDL-C-associated vascular protection to provide a clinically meaningful model, rather than being merely another blood-count ratio.

3.5 Subgroup Analysis

The ROC-derived NHR cutoff of 4.724 was employed to conduct prespecified subgroup analyses for sex, age, hypertension, diabetes mellitus and baseline NIHSS severity. Figure 3 shows the subgroup-specific odds ratios and interaction tests.

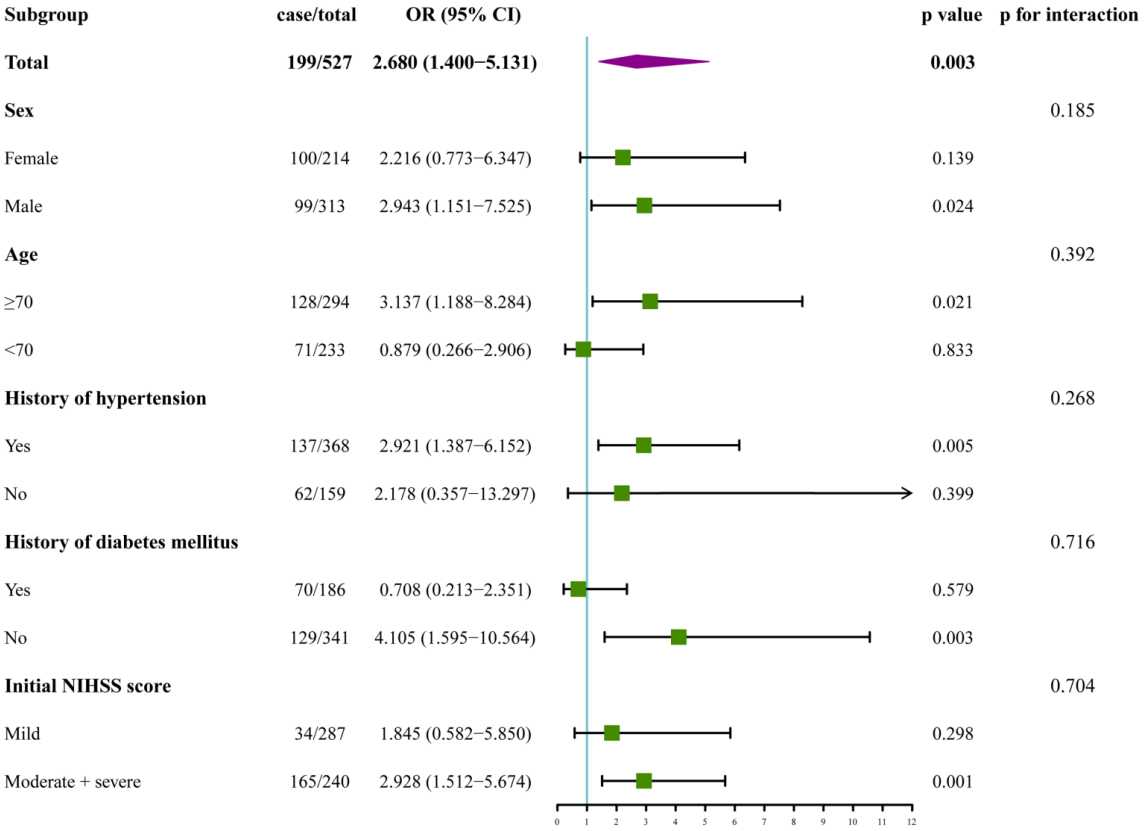

Figure 3: Subgroup Analysis of the Association Between Elevated NHR and Poor Prognosis in AIS Patients.

As shown in Figure 3, an increased NHR was associated with a poor outcome in men, older than 70 years old, hypertensive patients, non-diabetic patients and patients with moderate- to severe baseline NIHSS scores. The total cohort estimate was OR 2.680 (95% CI 1.400-5.131, p = 0.003). Interaction tests were not statistically significant for sex, age, hypertension, diabetes mellitus, or NIHSS strata, and thus no statistical evidence suggested that the NHR-outcome relationship was limited to a single subgroup. Subgroup patterns are clinically useful because the significant strata generally correspond to patients with a high vascular risk burden or severe neurological damage.

4 Discussion

Admission to NHR was associated with a 90-day functional outcome for patients with a first episode of AIS in this study. The Association was also still statistically significant in the adjusted continuous model, and the ROC analysis showed that NHR had better performance

than most other inflammatory indicators and was still statistically close to NLR. Therefore, NHR can be used to help identify individuals with a high risk of heart disease early. Therefore, the result should be considered a risk stratification rather than an indication of causality, and in retrospect, we cannot determine whether a reduction in NHR would lead to improved functional outcomes.

The Biology supports a paired structure for the ratio. Neutrophil increase after ischaemic injury may be due to enhanced activation of innate immunity, endothelial adhesion, oxidative stress, protease release, microvascular occlusion and blood-brain barrier damage. A decrease in HDL-C harms reverse cholesterol transport, damages endothelial cells, weakens antioxidant defence mechanisms, reduces leukocyte adhesion, etc. Therefore, a high NHR is likely associated with both inflammatory activation and weakened lipid-related vascular defence. The two signals may be responsible for NHR's superior performance in the absence of ratios involving inflammation, nutrition or clotting.

The initial attributes also support the above analysis. Neutrophil count increased and HDL-C decreased across the NHR quartiles in a clear gradient. The highest NHR quartile also had a larger proportion of large-artery atherosclerosis, higher CRP and fibrinogen, and poorer outcomes. This pattern shows that the high NHR was not due to a single laboratory abnormality. It is a vascular-inflammatory phenotype that can occur in AIS clinically, especially in the presence of large-artery atherosclerosis and systemic coagulation-inflammation activity.

According to outcome-stratified analysis, those with a poor prognosis were older in age, had a more severe NIHSS score, had an elevated neutrophil count, lower HDL-C, and higher NHR. The above differences are in line with the clinical course of AIS; therefore, neurological severity should continue to be the main index of functional improvement, and inflammatory and lipid-related markers may also offer supplementary data. Therefore, the sequence of the tables was arranged in accordance with the analytic logic: Table 1 shows NHR-based exposure stratification; Table 2 compares favourable and adverse outcomes; Table 3 tests for adjusted associations; and Table 4 compares the discriminatory performance of NHR with other inflammatory indices.

Interpretable Regression results need to be obtained. Risk was relatively high in the fourth quarter of the crude quartile model. After adjustment, the quartile estimates were reduced and no longer significant; in fact, adding clinical severity and laboratory indicators to the model further reduced the size of the effect. Continuous NHR was not significantly changed after adjustment. Therefore, the conclusion should focus on the continuous association and ROC-derived cutoff rather than stating that the highest quartile independently predicted a poor outcome in the fully adjusted quartile model. Therefore, this distinction will not be presented as a categorical result and will be in line with the displayed data.

ROC comparison to determine marker superiority. FAR, CAR, PAR and MHR performed poorly on this dataset; that is to say, albumin-, platelet- or monocyte-centred ratios were less closely associated with 90-day functional prognosis than neutrophil-centred ratios. NLR and NHR were the two highest indices, and both include neutrophil counts, so they were expected to be high. NLR regulates the innate immune system and lymphocyte-mediated regulation; NHR reduces neutrophil-induced inflammation and the vascular protective effects of HDL-C. The same AUC values indicate that NHR should not be used to replace NLR. It can be regarded as a parallel lipid-inflammatory index and is likely to offer more specific information on the atherosclerotic process or dyslipidemia in patients.

The cutoff of 4.724 should be understood as a cohort-derived risk threshold rather than an all-encompassing diagnostic boundary. It converts a continuous laboratory ratio into an interpretable screening flag. Patients above this threshold had an increased risk of poor 90-day recovery and thus required more frequent neurological examinations, medication adjustments,

rehabilitation plan revisions and subsequent follow-up. However, a lower cutoff does not mean that patients below the threshold are low-risk; NIHSS severity, atrial fibrillation, cardioembolic etiology, age and comorbidities are all still affecting outcomes. Therefore, NHR will be used as a supplementary indicator rather than an independent sorting tool.

The subgroup analysis offers some clinical ideas but is not a proof of effect modification. Males, older age, hypertension, non-diabetes, and medium-to-high NIHSS scores were all significantly associated with the outcome. There was no interaction effect. Therefore, the subgroup analysis identified certain subgroups where the association was more pronounced given the limited sample size, but this finding did not meet the standard for statistical significance and thus could not be reliably extended to other subgroups. NRH will likely be used early on for patients with an increased risk of vascular disease or serious neurological problems who need close observation in practice.

The included population will not be generalizable. The cohort included first-episode AIS patients who had not been exposed to antiplatelet or statin drugs recently and had not received thrombolytic therapy. The Design reduces several sources of laboratory confounding. Recent statin therapy can alter HDL-C and the inflammatory state; antiplatelet drugs are likely to affect platelet-associated ratios; and thrombolysis may be associated with either treatment-related inflammation or bleeding. Therefore, the constraint will make the NHR-outcome association of the observational biomarker analysis clearer. The Trade-off has less general applicability. The results apply most directly to non-thrombolysed, first-episode AIS patients with early hospital admission and complete follow-up, and are not suitable for reperfusion-treated large-vessel occlusion cohorts or recurrent stroke populations.

Some shortfalls persist. First, a single-center retrospective study may have selection bias, even if the inclusion and exclusion criteria are set in advance. Second, only NHR at the time of admission was measured; no changes during the acute and subacute stages were observed. Third, nutritional status, infection biomarkers not included in routine laboratory tests, infarct volume, vessel imaging parameters, reperfusion status, rehabilitation intensity and medication adherence were not fully incorporated into the model. Fourthly, the AUC of 0.716 shows moderate discrimination and is therefore not suitable for standalone clinical decisions. NHR can serve as a low-cost tool to assess the severity of illness in the clinic and should not replace imaging, NIHSS scoring, etiological classification or comprehensive assessment of vascular risk factors.

Verify that the raw-data table corresponds to the analysis in the spreadsheet prior to submission. Two of them are relatively significant. The initial screening denominator should be the same in the text and the flow diagram. In addition, the uric acid row of the quartile table should be verified as several subgroup values are inconsistent with the unit and the total-row distribution. The above checks need to be carried out in the source dataset and are not inferred during language revision.

In the future, it will be known whether several NHR values can improve the prognosis of patients after being hospitalized. AIS changes over hours and days, and a rise in neutrophil count can be due to infarct expansion, infection, stress hyperglycemia or other tissue injury. HDL-C may also be affected by an acute-phase response and nutrition. An altered NHR trend, such as a sustained increase in the first three days after hospitalisation or a failure to decline before discharge, may be associated with a poorer outcome compared to the starting NHR. Future prediction models will further explore whether NHR improves the discriminatory power or calibration among age, NIHSS score, TOAST subtype, atrial fibrillation, blood pressure, glucose, infarct volume, vascular occlusion site, collateral status, early neurological deterioration, in-hospital medication and rehabilitation exposure. The NHR is not yet a clinical

decision rule; therefore, a calibration plot and a decision curve analysis need to be performed first, as well as external validation.

5 Conclusions

Admission NHR is associated with poor 90-day functional outcomes in the first episode of AIS patients. The ratio had a moderate degree of discrimination and performed better than most other test-derived composite inflammatory indices, although it was close to that of NLR. NHR can be obtained through a general blood test of a complete blood count and lipid profile, and thus high-risk patients for AIS can be identified early for follow-up. Before NHR is applied as the decision threshold in clinical practice, external validation and repeated-measures analyses, as well as models that include imaging and treatment variables, need to be developed.

Author Contributions

J.C. and W.X. proposed the study concept. J.C. carried out the statistics and prepared the first version of the paper. R.W. and W.C. carried out research and data verification. L.L. Provided data curation services. W.X. has revised and modified the paper, given directions, and taken charge of the project. All the authors have read and approved the final paper.

Ethical Compliance

The Ethics Committee of Suining Central Hospital has approved the study (KYLLKS20240011). In line with the relevant provisions of the institution, this study was carried out. Waiver of informed consent was granted for this retrospective analysis of de-identified clinical data.

Conflicts of Interest

The authors declare that they have no other financial interests or commercial ties that might have affected the work published in this paper.

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