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The impact of inflammatory markers on clinical outcomes in acute ischemic stroke patients following mechanical thrombectomy: A multicentre study

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ABSTRACT

Background: Inflammation contributes to brain injury in acute ischemic stroke, but its role among patients treated with mechanical thrombectomy (MT) for large vessel occlusion (LVO) has not been fully established. The aim of this study was to explore the relationship between functional prognosis and the neutrophil-to-lymphocyte ratio (NLR) and derived ratios in patients undergoing MT.

Methods: This is a multicentre retrospective analysis of 970 consecutive patients treated with MT. Blood samples were collected on admission and after 24 h. Logistic regression was performed to assess the relationship between the ratios and 90-day modified Rankin scale (mRS) 0–2. Receiver-operating-characteristic (ROC) curves were used to estimate the ability of NLR and other ratios to predict the outcome. Restricted-cubic-spline (RCS) was used to investigate the association between NLR and 90-day mRS 3–6 and to determine a critical threshold.

Results: The 24-h NLR showed the strongest predictive performance (AUC = 0.670 alone; AUC = 0.784 when combined with other clinical variables) in patients treated with MT. An optimal NLR cutoff of 4.30 was identified, with patients below this threshold less likely to have poor 90-day outcome (RR 0.76 [95 % CI 0.65–0.89] $p = 0.001$) and significant shift toward better 90-day mRS scores (cOR 0.55, 95 %CI 0.40–0.74; $p < 0.001$). Restricted cubic spline analysis confirmed the cutoff's significance in predicting unfavourable mRS shifts.

Conclusions: This study highlights the 24-h NLR as a powerful predictor of stroke outcomes post-MT, with a threshold of 4.30 strongly associated with poor prognosis. These findings suggest that NLR can guide personalized treatment approaches to improve recovery trajectories.

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1. Introduction

Inflammation following an acute ischemic stroke is a critical factor contributing to brain injury, prompting investigations into various inflammatory biomarkers in stroke patients [1,2]. The post-stroke immune response is a multifaceted process characterized by the activation of diverse inflammatory cells and potential immunodepression [3]. Among the different leukocyte subtypes, neutrophils and lymphocytes may be associated with differential effects on clinical outcomes [4,5]. Indeed, the neutrophil-to-lymphocyte ratio (NLR) and its derived indexes have emerged as prognostic markers for mortality within various cardiovascular conditions and peripheral arterial occlusive disease [6,7]. Subsequent studies have suggested the prognostic relevance of NLR and its derived indexes in predicting mortality among acute ischemic stroke patients [8,9]. Indeed, elevated NLR levels have been independently linked to poorer outcomes at three months for ischemic stroke patients who have received intravenous thrombolytic therapy (IVT) or mechanical thrombectomy (MT) [10–15]. Nonetheless, the relationship between NLR, its derived indexes and functional outcomes in stroke populations has been studied in a relatively narrow context, with lack of homogeneity in the inclusion and exclusion criteria and the timing of blood sample collection. Moreover, numerous previous studies did not adequately exclude patients with potential confounding factors, such as concomitant infections, which may have introduced bias in the interpretation of the results. Therefore, there is a critical need to further investigate the role of the NLR and its derived indexes in acute ischemic stroke patient outcomes by employing standardized methodologies, defining inclusion criteria, and addressing confounding variables to enhance our understanding of the factors influencing these patients' prognosis. Therefore, in our multicentre study, we aim to investigate the association between NLR and its derived indexes and 90-day clinical outcomes in patients undergoing MT for acute ischemic stroke due to large vessel occlusion (LVO). We hypothesized that, consistent with existing literature linking the NLR to worse clinical outcomes, a similar association would persist in patients with large vessel occlusion ischemic stroke undergoing MT, even after excluding potential confounding factors or conditions associated with systemic infection or inflammation.

2. Methods

2.1. Study design and patients

This was a multicentre, observational, investigator-initiated, retrospective study, that included all acute stroke patients aged 18 years or older consecutively treated with MT in four thrombectomy centres: Charing Cross Hospital, Imperial College Healthcare NHS Trust, London (UK); St George's University of London, London (UK); Udine University Hospital, Udine (Italy);and Boston University, Boston (USA); between January 1st, 2016 and 30th March 2023 with local stroke registries available [16–19]. The study was conducted in accordance with the recommendations of World Medical Assembly (Helsinki 1964 and later revisions).

2.2. Patient inclusion and exclusion criteria for the analysis

The criteria for patient selection were: (1) age $\geq$ 18 years; (2) National Institutes of Health Stroke Scale (NIHSS) score 6 or more; (3) Alberta Stroke Program Early CT score (ASPECTS) 5 or more; (4) LVO sites: distal internal carotid artery, middle cerebral artery segments M1 or M2; (5) initiation of the MT had to be possible within 6 h after stroke onset; (6) pre-event modified Rankin Scale (mRS) score of 0 to 2. Intravenous thrombolysis (IVT) with intravenous tissue plasminogen activator (tPA) was administered in all patients who presented within 4.5 h of stroke symptom onset and without contraindications according to guidelines [20]. For this analysis, we excluded stroke patients with basilar artery occlusion and patients that met DAWN or DEFUSE 3 eligibility criteria [21,22]. Moreover, for the purpose of this analysis we excluded patients with a concomitant condition thatcouldpotentiallyalter the inflammation biomarkers, in particular: 1)ongoing effect of immunomodulatory or immunosuppressive drugs, 2) ongoing infections or infections developed within 48 h after admission, 3) chronic inflammatory diseases, 4) haematological disorders, 5) cancers (active and/or under treatment), 6) major traumas or surgical procedures in the previous 28 days, 7) acute myocardial infarction (AMI) with or without ST elevation, 8) severe liver or kidney dysfunction (eGFR $<$30 ml/min) as per literature references [23,24] and 9) recent transfusion ($<$ 7 days before admission) or transfusion done within 24 h after admission.

2.3. Data collection

The clinical information was collected prospectively including demographics, medical history (hypertension, diabetes mellitus, atrial fibrillation, hyperlipidemia, coronary heart disease, heart failure, transient ischemic attacks (TIAs), or stroke, or intracranial hemorrhage), smoking status, estimated time of symptom onset to admission, estimated time of symptom onset to needle for patients undergoing IVT, estimated time of admission to needle for patients undergoing IVT, estimated time of symptom onset to LVO groin puncture, estimated time of admission to LVO groin puncture and estimated time of symptom onset to recanalization. We also collected National Institutes of Health Stroke Scale (NIHSS) score on admission, laboratory information, imaging information, pre-stroke model of care (mothership/drip-and-ship), type of treatment, type of anesthesia, complications, and functional outcomes. The NIHSS score was used to evaluate neurological impairment. The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was used to determine early ischemic changes [25].

2.4. Blood samples

Venous blood samples were obtained from all patients at admission and after 24 h. Analyses of inflammatory markers—including the white blood cell (WBC) count, neutrophil count (N), platelet count (P), lymphocyte count (L) and monocyte (M)—were conducted in the local laboratory department. Laboratory measurements were performed within 60 min after the onset of blood collection. The NLR was determined as N/L in the respective collection timings; SIRI was defined as $N \times (M/L)$ in the respective collection timings; SII was defined as $P \times [N/L]$in the respective collection timings; PLR defined as P/L in the respective collection timings; finally, MLR was defined as M/L in the respective collection timings.

2.5. Assessment of clinical outcomes

The modified Rankin Scale (mRS) score was evaluated by local neurologists. Unfavourable functional outcome was defined as an mRS score between 3 and 6 at 90 ($\pm$14) days while favourable outcome was defined as an mRS score between 0 and 2 at 90 ($\pm$14) days. We also evaluated the mortality rate within 90 days and symptomatic intracerebral hemorrhage (sICH) within 3 days. Revascularization was determined using the modified thrombolysis in cerebral infarction (TICI) classification [26]. Successful recanalization was defined as grade 2b, 2c or 3 of recanalization. Early neurological improvement after MT was considered if there was a NIHSS lowering $\geq$4 between before MT and 24 h after.Early neurological deterioration was definedas NIHSS increase $\geq$4 in the same period of time [27,28].

Hemorrhagic transformation (HT) was considered as present if it was not seen on the admission brain scan with or without a decline in neurological status including all subtypes following the Heidelberg classification [29].

sICH was identified as any intracranial hemorrhage on neuroimaging

with a ⩾4 point increase of the NIHSS score from baseline [30].

2.6. Statistical analysis

Variables were compared with the chi-square test for frequency data, Mann–Whitney *U* test for skewed data, or *t*-test for normal data, as appropriate. Results were shown as either mean value±standard deviation (SD) for normal data or median and interquartile range (IQR) for skewed data. *P*-values were considered statistically significant at <0.05. We first conducted a crude logistic regression analysis to examine the unadjusted association of those markers with favourable outcome (mRS score between 0 and 2) at 90 days. Variables with a significant association with this study outcome ($P \leq 0.05$) were considered for multivariate logistic regression analysis with statistical significance set at a $P < 0.05$.Adjusted odds ratios (ORs) with 95 % confidence intervals (CIs) were obtained. The predictive ability of inflammatory markers for clinical outcomes was defined by the area under the curve (AUC) in receiver operating characteristic (ROC) analyses. The predictive model included the variables independently associated with 90-day favourable outcome after multivariate analysis. No pre-specified variables were added to the ROC analysis to enhance the model's accuracy. ROC curves were compared using the DeLong test. Data are displayed in tables as median and interquartile range (IQR) unless otherwise specified. All probability values were two-tailed. Statistical significance was set at a *p*-value of <0.05. We further evaluated the pattern and magnitude of associations between 24-h NLR and the risk of unfavourable functional outcomes using restricted cubic splines (RCSs) with knots at the 25th, 50th, 75th, and 95th percentiles. The cutoff value associated with the 50th percentile of risk was determined using logistic regression. The analysis was adjusted for covariates, including age, hypertension, hypercholesterolemia, known atrial fibrillation, diabetes, previous ischemic stroke/TIA, current smoking, ASPECTS, NIHSS on admission, general anesthesia, admission glycemia, onset-to-needle time, sICH, admission hemoglobin, and 24-h CRP, with TICI≥2b as a procedural success indicator. A weighted ordinal logistic regression (shift analysis) with a robust estimator explored mRS shift at 90-days in treated patients with values of 24 h-NLR < vs ≥ the determined cut-off alongside pre-specified clinical variables of interest (Age, sex, NIHSS, hypertension, coronary artery disease, smoking, ASPECTS, general anesthesia, model of care, TICI score).Subgroup analysis of 90-day unfavourable functional outcomepopulation was performed in pre-defined subgroups of interest. We used a logistic regression model with 24 h NLR, subgroup variable, and their interaction term as independent variables to determine the homogeneity in the effect of 24 h NLR by each subgroup variable. The *p* value was presented for the interaction term. Lastly, marginal effects analysis was employed to visualize and exanimate predicted probabilities of 90-day unfavourable functional outcoments across the range of 24 h NLR within each subgroup.Statistical analyses were performed with SPSS statistical software (v.22, IBM Inc.), MedCalc version 22.021 for Windows and RStudio (ver 2024.4, RStudio PBC).

3. Results

Overall, 970 patients with acute ischemic stroke due to LVO undergoing MT were included in our study analysis (see study algorithm Fig. 1). Table 1 shows the demographic and clinical characteristics of the patients with 90-day favourable vs unfavourable outcome. Patients with 90-day unfavourable outcome were older ($p < 0.001$), had more often hypertension ($p < 0.001$), diabetes ($p = 0.01$), hypercholesterolemia ($p = 0.03$), known atrial fibrillation ($p = 0.05$), and previous TIA/ischemic stroke ($p = 0.05$) and were more often on treatment with antiplatelet therapy prior to the index event ($p = 0.01$). Conversely, patients with 90-day favourable outcome were often smokers ($p = 0.001$). The two groups had a significant difference in NIHSS on admission, respectively 18 (13–22) for patients with poor 90-day outcome and 16 (10–20) for patients with good 90-day outcome ($p < 0.001$). The two groups differed significantly in terms of the distribution of TICI score post MT ($p < 0.001$), median NIHSS score at 24 h ($p < 0.001$), rate of early

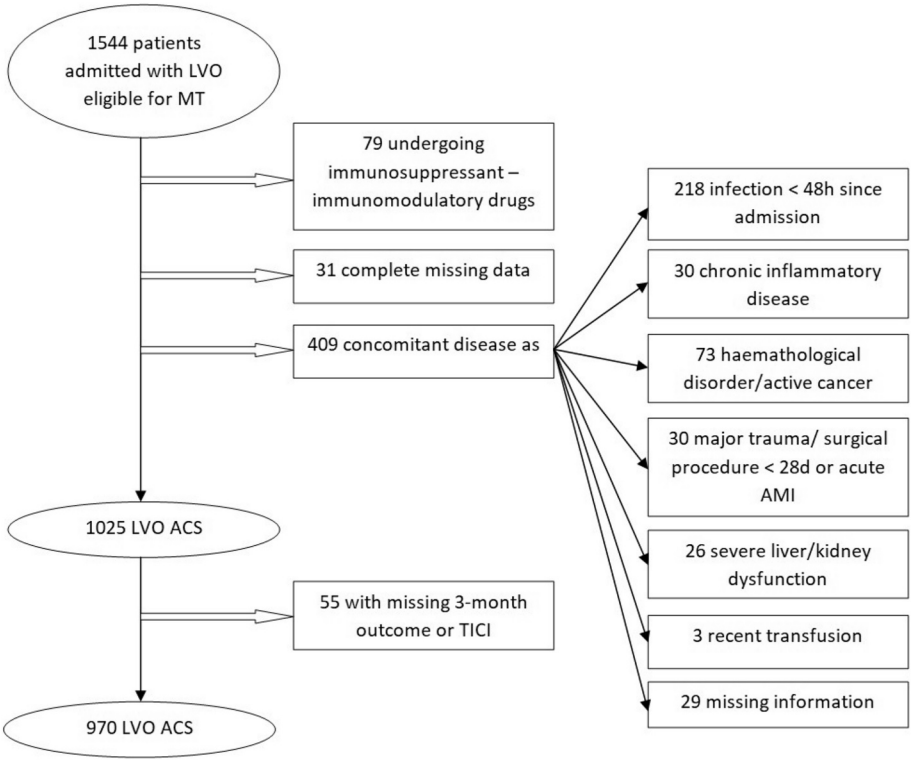

Fig. 1. Study algorithm.
ACS: anterior circulation strokes; LVO: large vessel occlusion; MT: mechanical thrombectomy, AMI: acute myocardial infarction (included ST elevation and non ST elevation myocardial infarction) TICI: modified thrombolysis in cerebral infarction classification.

Table 1
Demographic, clinical characteristics and outcomes. Bold values are consiedered significant (p < 0.05).

	Overall population (*N* = 970)	90- day Unfavourable outcome (mRS ≥ 3) (*N* = 543)	90-day Favourable outcome (mRS ≤ 2) (*N* = 427)	p
Demographics				
Age, years [median (IQR)]	69 (56–78)	72 (59–80)	64 (54–74)	**<0.001**
Female sex [n, (%)]	454 (47)	262 (48)	192 (45)	0.309
Hypertension [n, (%)]	538 (56)	336 (62)	202 (47)	**<0.001**
Diabetes mellitus [n, (%)]	195 (20)	126 (23)	69 (16)	**0.007**
Hypercholesterolemia [n, (%)]	339 (35)	206 (38)	133 (31)	**0.028**
Known Atrial fibrillation [n, (%)]	251 (26)	154 (28)	97 (23)	**0.046**
AFDAS [n, (%)]	177 (18)	105 (19)	72 (17)	0.322
Coronary artery disease [n, (%)]	155 (16)	96 (18)	59 (14)	0.103
Congestive heart failure [n, (%)]	78 (8)	47 (9)	31 (7)	0.427
Current smoking [n, (%)]	159 (16)	70 (13)	89 (21)	**0.001**
ETOH [n, (%)]	122 (13)	63 (12)	59 (14)	0.302
Previous TIA/ischemic stroke [n, (%)]	160 (17)	101 (19)	59 (14)	**0.046**
Previous ICH [n, (%)]	7 (1)	3 (1)	4 (1)	0.706
Admission therapy				
Anticoagulation on admission [n, (%)]	126 (13)	74 (14)	52 (12)	0.505
Antiplatelet therapy on admission [n, (%)]	195 (20)	125 (23)	70 (16)	**0.011**
Stroke characteristics				
Known onset [n, (%)]	813 (84)	447 (82)	366 (86)	0.154
Pre stroke care [n, (%)]				0.225
Mothership	379 (39)	203 (37)	176 (41)	
Drip-and-ship	591 (61)	340 (63)	251 (59)	
NIHSS on admission [median (IQR)]	17 (12−21)	18 (13–22)	16 (10–20)	**<0.001**
TICI≥2b after MT [n, (%)]	885 (91)	470 (87)	415 (97)	**<0.001**
NIHSS 24H [median (IQR)]	9 (4–16)	12 (7–19)	5 (3−11)	**<0.001**
Early neurological improvement	563 (58)	260 (48)	303 (71)	**<0.001**
Early neurological deterioration	105 (11)	80 (15)	25 (6)	**<0.001**
Post MT Hemorrhagic transformation [n, (%)]	262 (27)	190 (35)	72 (17)	**<0.001**
sICH [n, (%)]	51 (5)	45 (8)	6 (1)	**<0.001**
90-day Mortality	156 (16)	156 (29)	0 (0)	

Legend: ETOH = ethanol abuse; TIA = transient ischemic attack; ICH = intra cerebral hemorrhage; NIHSS = National Institutes of Health Stroke Scale. AFDAS = atrial fibrillation detected after stroke. sICH: symptomatic intracerebral hemorrhage, TICI: modified thrombolysis in cerebral infarction classification.

neurological improvement (p < 0.001), deterioration (p < 0.001), rate of post MT hemorrhagic transformation (p < 0.001) and sICH (p < 0.001). Overall, in our patient sample the 90-day mortality was 16 %.

Table 2 shows the comparison of the procedural features. The unfavourable outcome versus favourable outcome groups differed in terms of baseline ASPECTSon admission (9 (7–10) vs 9 (8–10), p < 0.001, respectively), type of anesthesia received during the MT (general anesthesia 82 % vs. 73 %, $p = 0.001$, respectively), onset-to-needle ($p = 0.03$) and onset-to-groin (p = 0.001) time.No significant differences were found in terms of site of occlusion ($p = 0.383$), rate of IVT ($p = 0.145$) and the other treatment metrics considered.

Table 3 reports blood tests collected on admission and at 24 h from the index event in patients with 90-day good and poor outcome. Of note, NLR, PLR, MLR, SIRI and SII on admission and at 24 h from the index event were significantly different between the two groups. The detailed comparisons between all the blood test variables can be found in Table s1 and (Fig. 2).

Table 4 shows the logistic regression analysis to determine the association between admission and 24 h NLR, PLR, MLR, SIRI, and SII and 90-day favourable outcome(mRS 0–2). The respective multivariate analyses were adjusted for the covariates as reported in Table S2. Our analysis shown that admission NLR (OR 0.917 CI95 % 0.835–0.986, $p = 0.02$), SIRI (OR 0.866 CI95 % 0.774–0.970, $p = 0.01$), SII (OR 0.999 CI95 % 0.998–0.999, $p = 0.04$),24 h NLR (OR 0.909 CI95 % 0.850–0.972, $p = 0.01$) and SII (OR 0.999 CI95 % 0.998–0.999, p = 0.02) were independent predictors of 90-day good functional outcome after MT. We also evaluated the association with sICH and 90-day mortality. After multiple adjustment, 24 h NLR (OR 1.110; CI95 % 1.063–1.158; $p < 0.001$), 24 h PLR (OR 1.003; CI95 %1.003–1.006; $p = 0.01$), 24 h SIRI (OR 1.115; CI95 %1.067–1.164; p < 0.001), 24 h SII (OR 1.001; CI95%1.000–1.001; p < 0.001) were significantly associated

Table 2
Procedural features. Bold values are consiedered significant (p < 0.05).

	Overall population (N = 970)	90- day Unfavourable outcome (mRS ≥ 3) (N = 543)	90-day Favourable outcome (mRS ≤ 2) (N = 427)	p
Site of occlusion [n, (%)]				0.383
Distal ICA	98 (10)	52 (10)	46 (11)	
M1	610 (63)	346 (64)	264 (62)	
M2	147 (15)	75 (14)	72 (17)	
Tandem occlusion	115 (12)	70 (13)	45 (11)	
General anesthesia [n, (%)]	757 (78)	446 (82)	311 (73)	**0.001**
Bridging therapy [n, (%)]	646 (67)	351 (65)	295 (69)	0.145
ASPECT score [median (IQR)]	9 (8–10)	9 (7–10)	9 (8–10)	**<0.001**
Timing (min) [median (IQR)]				
Onset-to-door	220 (97–286)	223 (127–290)	211 (82–276)	0.146
Onset-to-needle	125 (97–161)	129 (100–167)	122 (95–159)	**0.031**
Door-to-needle	44 (31–60)	44 (32–60)	44 (30–58)	0.399
Onset-to-groin	259 (205–325)	273 (212–334)	245 (195–310)	**0.001**
Door-to-groin	83 (45–126)	83 (45–132)	83 (44–124)	0.251
Onset to Recanalisation	291 (129–371)	312 (151–384)	273 (129–362)	0.146

Legend: TICI = modified thrombolysis in cerebral infarction classification; ICA = internal carotid artery; M1, M2 = middle cerebral artery segments M1 or M2. ASPECT score: Alberta Stroke Program Early CT score.

Table 3
Blood test.

	Overall population (N = 970)	90- day Unfavourable outcome (mRS ≥ 3) (N = 543)	90-day Favourable outcome (mRS ≤ 2) (N = 427)	p
Admission test[median (IQR)]				
NLR	4.54 (2.27–8.27)	5.00 (2.67–9.33)	4.06 (2.00–7.38)	<0.001
PLR	156.35 (102.20–230.00)	165.38 (109.47–241.11)	142.67 (94.78–223.66)	0.001
MLR	0.38 (0.27–0.55)	0.42 (0.29–0.60)	0.35 (0.25–0.50)	<0.001
SIRI (x 10^9/l)	2.34 (1.23–4.32)	2.65 (1.40–4.82)	2.09 (1.08–3.80)	<0.001
SII (x 10^9/l)	959.16 (494.63–1827.97)	1118.81 (569.75–1946.50)	829.26 (424.34–1665.52)	0.001
24 h test[median (IQR)]				
NLR	5.68 (3.75–8.80)	6.51 (4.27–10.00)	4.47 (3.13–6.54)	<0.001
PLR	155.71 (112.73–222.2)	168.00 (121.25–242.22)	143.33 (105.33–183.33)	<0.001
MLR	0.53 (0.36–0.75)	0.58 (0.42–0.85)	0.44 (0.33–0.64)	<0.001
SIRI (x 10^9/l)	3.66 (2.22–6.19)	4.37 (2.66–7.50)	2.77 (1.78–4.73)	<0.001
SII (x 10^9/l)	1106.41 (682.35–1820.89)	1321.91 (768.50–2065.33)	892.00 (600.00–1485.08)	<0.001

Legend: WBC = white blood count, RBC = red blood count, Hb = hemoglobin, PLT = platelets, ESR = erythrocyte sedimentation rate, CRP = C reactive protein, NLR = neutrophil-to-lymphocyte ratio, PLR: platelets to lymphocyte ratio; MLR: monocyte to lymphocyte ratio, SIRI: Systemic Inflammation Response Index; SII: systemic immune-inflammation index.

with sICH. The same ratios were associated with mortality: 24 h NLR (OR 1.065; CI95%1.020–1.111; p = 0.01), 24 h PLR (OR 1.002; CI95% 1.001–1.004; $p = 0.04$), 24 h SIRI (OR 1.047; CI95%1.001–1.095; $p = 0.05$), 24 h SII (OR 1.001; CI95%1.000–1.001; p = 0.01).

Using the ROC curves from the logistic regression analysis, we identified the predictive accuracy of age, ASPECTS, GA, sICH, Glycemia, TICI≥2b, admission NLR, SIRI and SII and 24 h NLR and SII, and combined models for predicting 90-day favourable outcome after MT. The AUCs for each clinical variable found significant in all the multivariate analysis were:age (AUC 0.613; IC95% 0.578–0.649), ASPECTS (AUC 0.599; IC95% 0.569–0.636), GA(AUC 0.547; IC95% 0.510–0.583), sICH (AUC 0.534; IC95% 0.500–0.571), Glycemia (AUC 0.655; IC95% 0.619–0.691), TICI≥2b (AUC 0.553; IC95% 0.517–0.589). The model combining age, ASPECTS, GA, sICH, Glycemia, TICI≥2b(CV) had an AUC of 0.750 (CI95% 0.717–0.783). Including 24 h-NLR in the previous model, we obtained the highest AUC 0.784 (CI95% 0.748–0.819) (Fig. 3) (Table s3 and s4). According to DeLong test, this latest model performed significantly better in predicting90-day good functional outcome as compared to the combined CV ($p = 0.05$).

We conducted a restricted cubic spline analysis to evaluate the relationship between the 24 h- NLR and 90-day poor outcome(mRS 3–6). Our analysis identified a significant association at the 50th knot, corresponding to a NLR value of 4.30. This specific threshold was found to be associated with a notable change in outcomes, with a *p*-value of <0.0001, indicating a highly statistically significant effect (Fig. 4).

Patients with acute ischemic stroke undergoing MT with 24 h-NLR ≥ 4.30showed a significantly lower risk of primary outcome (mRS 0–2) (adjusted risk ratio 0.76 [95 % CI 0.65–0.89]; $p = 0.001$) compared with their counterparts with 24 h-NLR < 4.30 (Table s5). We found significant differences in the 90- day ordinal distribution of mRS scores (adjusted OR 0.55 [95 % CI 0.40–0.74]; $p < 0.001$) confirming the 24 h NLR cut-off of 4.30as an effect modifier for worse outcome after MT in patients with acute ischemic stroke. (Fig. 5).

The adjusted margin plots for analyzing24 h NLR and 90-day unfavourable functional outcome in different subgroups with multivariable binary logistic regression are reported in Fig. 6. We found a significant interaction between 24 h NLR and bridging therapy in predicting unfavourable functional outcome at 90 days (*P*-values for interaction: mRS3–6 = 0.045). We found no interaction between 24 h NLR and age, pre-hospital model of care and NIHSS severity (respectively P-values for interaction: mRS3–6 = 0.105, 0.259, 0.277).

Finally in Tables S6, S7 and S8, we explored the predictors of 24-h NLR at the cut-off of 4.30 and above. Multivariate logistic analysis (Table S9) documented that coronary artery disease (OR 1.883; CI95% 1.145–3.097;$p = 0.01$), current smoking status (OR 0.599; CI95% 0.384–0.932; $p = 0.02$), pre-stroke care (OR 1.515; CI95% 1.081–2.123; p = 0.02), ASPECTS (OR 0.838; CI95% 0.735–0.956; $p = 0.001$), GA (OR 1.878; CI95% 1.243–2.837; p = 0.001), and the efficacy of recanalization, quantified as a TICI score of ≥2b following mechanical thrombectomy (OR 0.244; CI95% 0.112–0.532; $p < 0.001$) were independent predictors of 24-h NLR of 4.30 in patients with acute ischemic stroke undergoing MT.

4. Discussion

In our multicentre analysis involving 970 patients with acute ischemic stroke due to anterior circulation LVO who underwent MT, we observed the following significant findings: (1) admission NLR, SIRI, SII and 24-h NLR and SII are all significantly associated with outcomes at 90 days post-MT treatment; (2) among these biomarkers, the 24-h NLR demonstrated the highest predictive performance regarding patient outcomes; (3) a 24-h NLR threshold of 4.30 was identified as a reliable cut-off for discriminating between patients likely to experience good versus poor outcomes at 90 days; and (4)the predictive value of this 24-h NLR cut-off is influenced by various pre-stroke characteristics, such as the presence of previous coronary artery disease and smoking status, as well as imaging outcomes and procedural features, including the ASPECTS and TICI score. These findings highlight the importance of both inflammatory markers and clinical characteristics in shaping functional recovery following MT.

Previous studies have explored the role of the NLR as a valuable prognostic indicator in patients experiencing acute ischemic stroke [11,31]. However, many of these studies have been limited by several critical factors. Notably, they often involved small patient samples, which may restrict the generalizability of their findings. Additionally, the majority of these studies were conducted as single-centre analyses, potentially introducing bias and limiting the applicability of the results to broader populations. Furthermore, many studies did not establish clearly defined inclusion and exclusion criteria, leading to potential confounding variables that could affect the interpretation of NLR as a predictive biomarker. Consequently, while the association between NLR and stroke outcomes is promising, there is a pressing need for larger, multi-centre studies with rigorous methodological frameworks to validate these findings and enhance the reliability of NLR as a prognostic tool in the context of acute ischemic stroke.

One of the main findings of our multi-centre study is that among the different biomarkers explored, the 24-h NLR demonstrated the highest predictive performance regarding acute ischemic stroke patient outcomes undergoing MT. Notably, we identified a 24-h NLR threshold of 4.30, below which patients demonstrated a significantly lower risk of

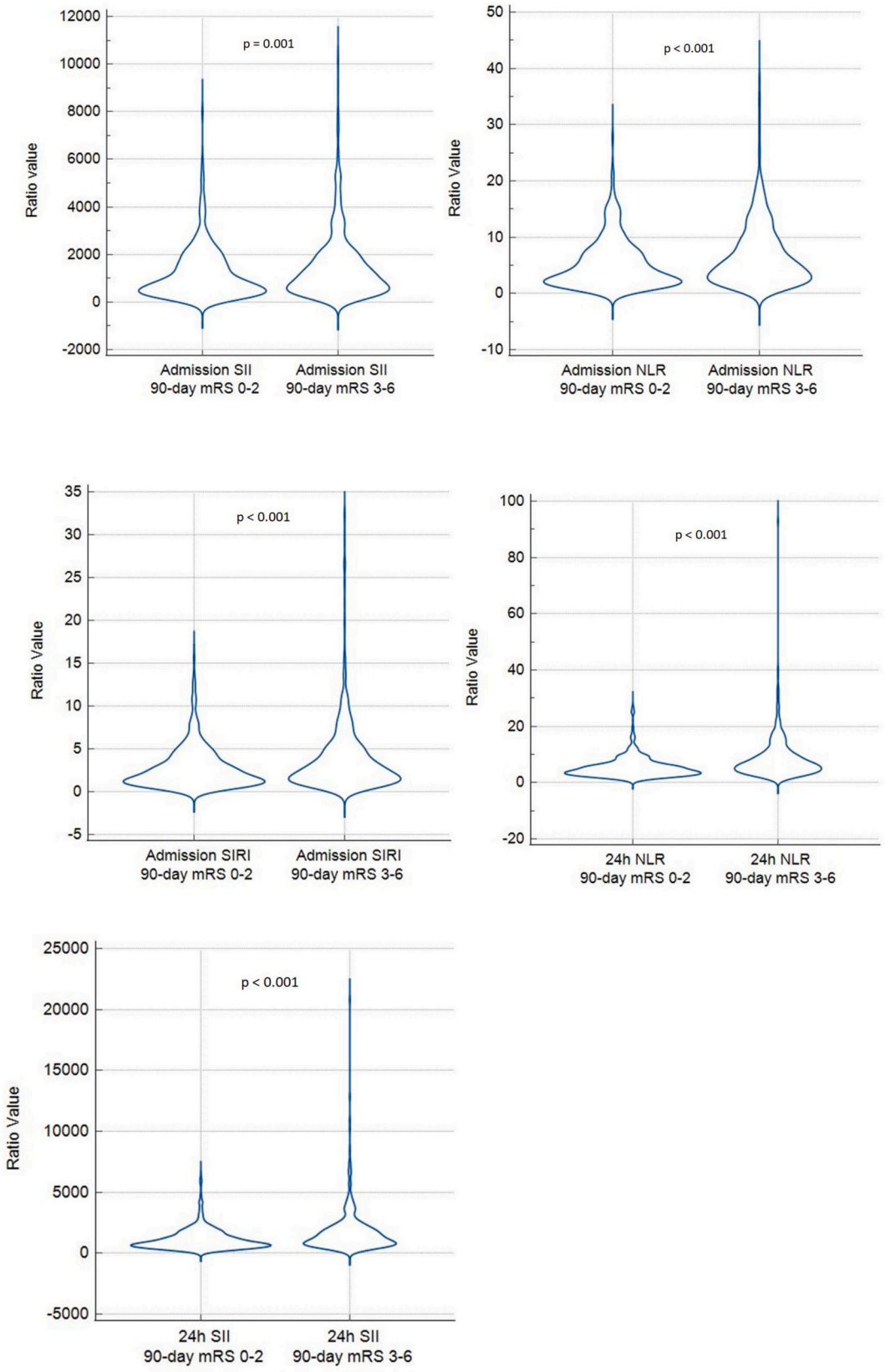

Fig. 2. violin plot for admission and 24 h ratios significantly associated with mRS 0–2.

Table 4
Multivariate analysis to predict prespecified outcomes (binary logistic regression). Bold values are consiedered significant ($p < 0.05$).

	Favourable outcome (90-day mRS 0–2)*			sICH†			90-day Mortality‡		
	OR	CI 95%	p value	OR	CI 95%	p value	OR	CI 95%	p value
Admission NLR	0.917	0.853–0.986	**0.019**	0.998	0.935–1.065	0.949	1.030	0.974–1.089	0.303
Admission PLR	0.996	0.986–1.001	0.228	1.001	0.998–1.003	0.692	1.001	0.998–1.003	0.456
Admission MLR	0.809	0.376–1.739	0.587	1.532	0.729–3.221	0.260	0.934	0.377–2.314	0.883
Admission SIRI	0.866	0.774–0.970	**0.013**	1.043	0.962–1.132	0.310	1.034	0.950–1.127	0.439
Admission SII	0.999	0.998–0.999	**0.035**	1.000	0.999–1.001	0.920	1.000	0.999–1.001	0.108
24 h NLR	0.909	0.850–0.972	**0.005**	1.110	1.063–1.158	**<0.001**	1.065	1.020–1.111	**0.004**
24 h PLR	0.997	0.994–1.000	0.059	1.003	1.001–1.006	**0.005**	1.002	1.001–1.004	**0.040**
24 h MLR	0.565	0.205–1.557	0.270	1.808	0.950–3.442	0.071	1.179	0.770–1.805	0.448
24 h SIRI	0.927	0.850–1.011	0.086	1.115	1.067–1.164	**<0.001**	1.047	1.001–1.095	**0.047**
24 h SII	0.999	0.998–0.999	**0.017**	1.001	1.000–1.001	**<0.001**	1.001	1.001–1.002	**0.005**

*adjusted for age, Hypertension, Hypercholesterolemia, Known atrial fibrillation, diabetes, previous ischemic stroke/TIA, current smoking, ASPECT score, NIHSS on admission, general anesthesia, admission glycemia, onset-to-needle time, sICH, admission Hb and 24 h CRP, TICI≥2b.
† adjusted for TICI≥2b, door to groin.
‡ adjusted for Hypertension, Hypercholesterolemia, Known atrial fibrillation, ASPECT score, NIHSS on admission, general anesthesia, admission glycemia, sICH, 24 h CRP, TICI≥2b.

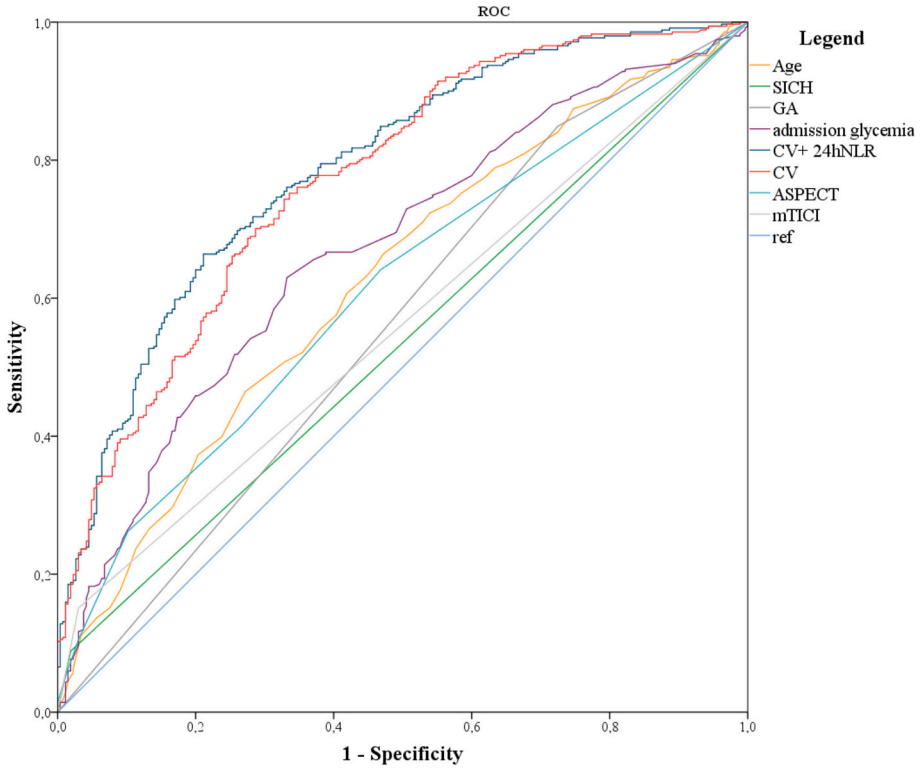

Fig. 3. ROC analysis to predict 90-day favourable outcome (mRS 0–2).
Note: CV = clinical variables (Age + ASPECTS+GA + sICH+Glycemia+mTICI). sICH: symptomatic intracerebral hemorrhage, mTICI: modified thrombolysis in cerebral infarction classification; GA = general anesthesia; ASPECT score: Alberta Stroke Program Early CT score; NLR: neutrophil to lymphocyte ratio.

poor functional outcomes, as measured by the modified Rankin Scale (mRS 3–6). This correlation underscores the notion that an elevated NLR, which reflects a heightened innate inflammatory response in the body, is associated with worse outcomes following an acute ischemic event.Our work is in line with the analysis of Lux et al. [10] that found that the 24 h-NLR is better associated to 90d outcome rather than admission NLR. Conversely, a retrospective analysis of the ATTENTION registry [32] reported that higher NLR on admission was significantly related to unfavourable functional outcome and mortality at 90 days in acute patients with basilar artery occlusion receiving MT. However, they also documented a significant interaction between increased NLR and bridging therapy on these outcome measures in line with our findings. It is noteworthy to mention that most of the previous studies reported only the admission NLR and they did not explore the dynamic change of white blood cells count following their activation and infiltration of ischemic tissue. As reported in the review of Jayaraj et al. [33], neutrophils peak between 1 and 3 days after stroke and then decline, together with a concomitant decrease of lymphocytes. Therefore, admission NLR testing can be normal or not clearly indicative of prognosis as the peak could be reached after 24 h from the acute ischemic event. The mechanism underlying this relationship between NLR and outcome following acute ischemic stroke may involve the role of neutrophils and lymphocytes in the inflammatory cascade following a stroke [34]. Neutrophils are among the first responders to sites of acute injury and are associated with inflammation. They secrete pro-inflammatory cytokines, release reactive oxygen species, and promote neuroinflammatory responses, all of which can exacerbate neuronal injury and influence neurovascular integrity [35]. Conversely,

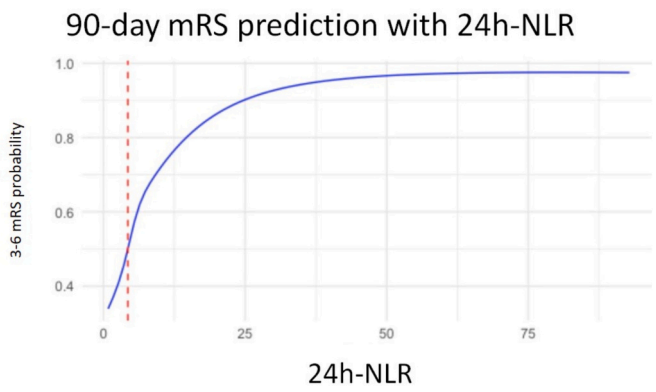

Fig. 4. restricted cubic spineline for the prediction of 90-day unfavourable outcome (mRS3–6).

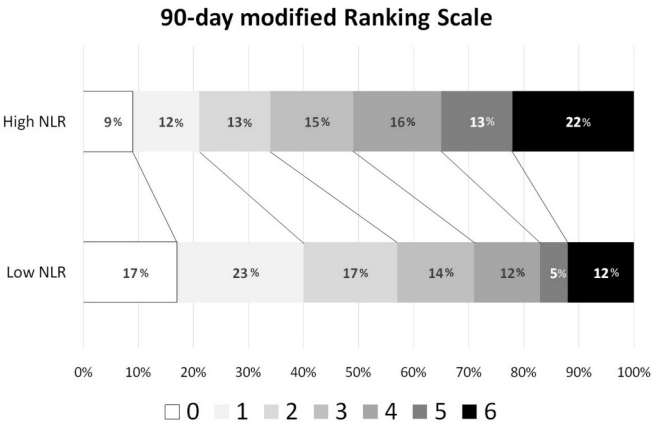

Fig. 5. mRS shift analysis for high and low 24 h-NLR level (cut off at 4.301).

lymphocytes, particularly T-cells, are crucial for modulating inflammation and promoting tissue repair [36]. An elevated NLR could thus indicate an imbalance in the immune response, where excessive neutrophil activity and reduced lymphocyte-mediated regulation culminate in detrimental effects on brain tissue. Understanding these factors is crucial for refining prognostic assessments and tailoring therapeutic strategies in this patient population.

One novel aspect of our analysis is that we investigated the independent predictors of high value of 24-h NLR after acute ischemic stroke with LVO. We documented that history of previous coronary artery disease is among the independent predictors of 24-h NLR above the threshold of 4.30after multivariate analysis. Inflammation following myocardial infarction (MI) plays a critical role in facilitating tissue repair during the acute phase and in chronic remodelling. However, this prolonged activation can have effects in other organs, such as the brain. Experimental models have demonstrated the activation of peri-vascular macrophages in cerebral vessels post-MI, with subsequent chronic heart failure appearing to trigger neuroinflammation [37–39]. These findings have also been substantiated in studies involving human subjects. Research indicates that a pre-existing inflammatory status can lead to an exaggerated response following a stroke or MI, influenced by elevated circulating cytokines [40]. In a recent study [41], the relationship between inflammatory biomarkers, including the NLR and high-sensitivity C-reactive protein (hsCRP), was examined over time. The authors found a significant association between NLR levels and the occurrence of major cardiovascular and cerebrovascular events during long-term follow-up, whereas hsCRP exhibited a weaker association in this context. These mechanisms are integral to the Heart-Brain Axis (HBA), which encompasses the complex interactions between the neuro-endocrine-immune systems and becomes particularly evident following ischemic events affecting either the brain or the heart [42,43].Moreover, systemic chronic inflammation initiated by MI [44] may expedite additional pathological processes, such as atherosclerosis and atrial fibrillation, which can precipitate acute ischemic stroke. In a recent study [41], the relationship between inflammatory biomarkers, including the NLR and high-sensitivity C-reactive protein (hsCRP), was examined over time. The authors found a significant association between NLR levels and the occurrence of major cardiovascular and cerebrovascular events during long-term follow-up, whereas hsCRP exhibited a weaker association in this context.

Interestingly, our analysis also demonstrates that both the ASPECTS and a successful Thrombectomy in Cerebral Ischemia (TICI) score after mechanical thrombectomy (MT) serve as significant independent predictors of 24-h neutrophil-to-lymphocyte ratio (NLR) levels.This relationship can be explained by the association between the extent of cerebral lesions and the resulting inflammatory response. Specifically, a reduced extent of injury corresponds to a diminished inflammatory response, as supported by previous findings. Consequently, inadequate recanalization may lead to a larger stroke volume, resulting in an increased inflammatory response. The study conducted by Kocaturk [45] found a correlation between elevated NLR values and stroke volume in cases of anterior circulation ischemic events. Furthermore, in a mouse model, Garau et al. [46] described a reduction in stroke volume following the administration of an anti-chemokine molecule. Conversely, one trial demonstrated no significant benefit on infarct volume or neurological outcomes from the infusion of a neutrophil inhibitory factor alongside thrombolytic therapy [47]. In contrast, smaller trials that evaluated pharmacological interventions targeting the adaptive inflammatory response reported improved stroke outcomes and reductions in stroke volume [48–50].These findings underscore the necessity for larger studies to further investigate the roles of both innate and adaptive inflammation, as well as immunomodulatory therapy in relation to stroke extent and associated patient outcomes. [51]

Finally, only a limited number of studies have investigated the association between platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune-inflammation index (SIRI), and systemic inflammation index (SII) levels with outcomes in patients undergoing mechanical thrombectomy (MT) [52,53]. These studies indicated that admission (or levels measured within 24 h) of SIRI and SII were associated with clinical outcomes and stroke complications. Our findings support the relevance of these derived ratios alongside the neutrophil-to-lymphocyte ratio (NLR); however, admission SIRI appears to have superior predictive performance compared to both admission and 24-h SIRI. Furthermore, both SIRI and SII demonstrate less robustness in predicting outcomes compared to the 24-h NLR. Additionally, the 24-h NLR was instrumental in enhancing the area under the curve (AUC) in the receiver operating characteristic (ROC) analysis compared to the cumulative assessment of all cardiovascular risk factors.

Our study has several limitations. First, the retrospective design may have introduced bias in the results. Second, we lacked data on collateral status, ethnicity, and stroke etiology, all potential confounders that could influence outcomes. Third, we did not collect data beyond the 24-h blood tests, which would have allowed for a more comprehensive assessment of the role of the ratios in the subsequent days. Despite our efforts, we cannot exclude that our results could have been influenced by an incomplete adjustment for patient characteristics in selecting the model for the multivariable analysis.

While our study involved a large, multicentre cohort and rigorous methodological approaches to reduce sample bias, we acknowledge the need for external validation of our findings. The observed differences in 90-day mRS 0–2 outcomes between the high and low NLR groups are notable, but such substantial effects from a single biomarker warrant confirmation in independent datasets. External validation using prospective cohorts from diverse populations and healthcare settings is crucial to confirm the reproducibility and generalizability of our results.

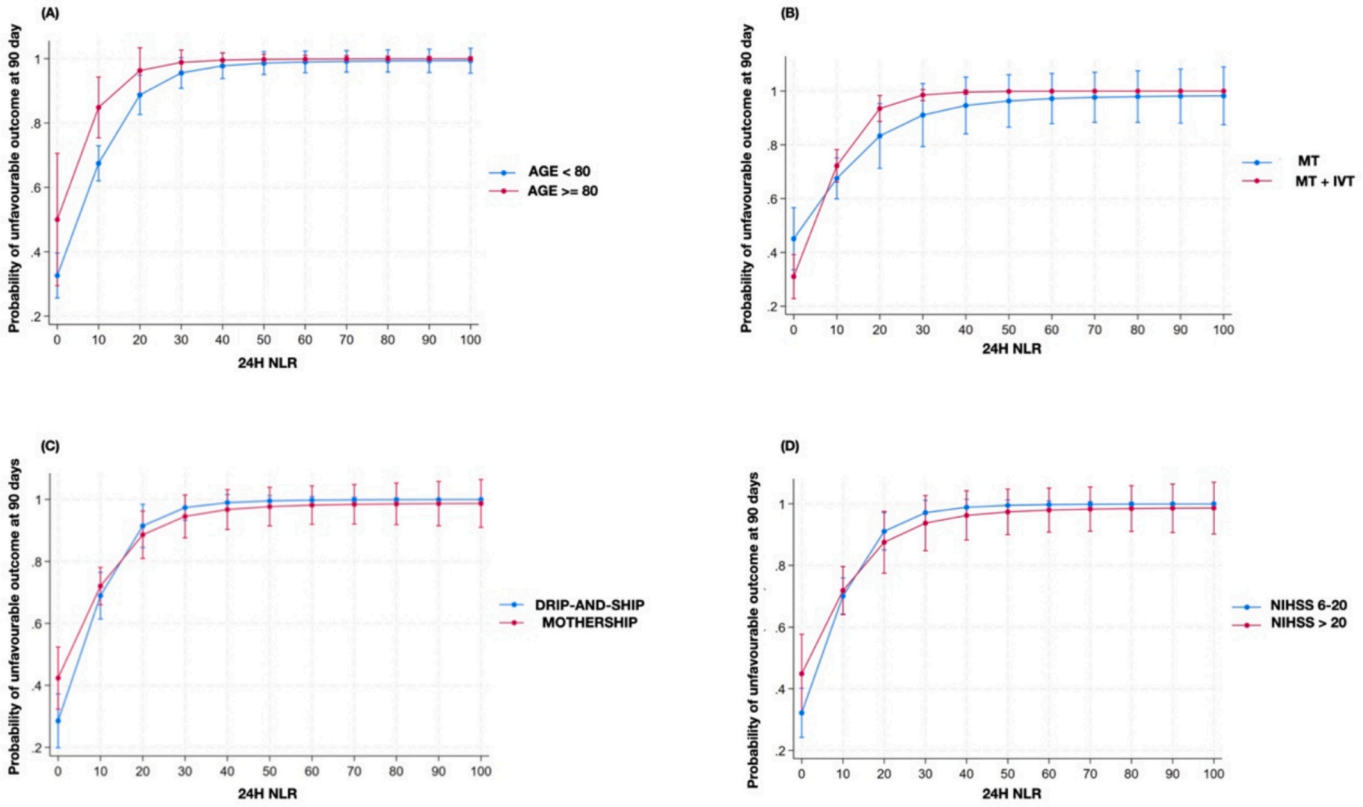

Fig. 6. The adjusted margin plots of 24 h - NLR with probability of 90-day unfavourable functional outcome (A) 24 h NLR and Age (B) 24 h NLR and MT versus bridging therapy (C) 24 h NLR and pre-hospital stroke care (D) 24 h and NIHSS severity. Each graph shows the predicted probability and 95% confidence interval (shade) of different outcomes.

Additionally, validation studies should explore potential regional, demographic, or treatment-related variations that could influence the association between NLR and clinical outcomes.

Despite these limitations, our analysis presents several strengths: (1) a large cohort of patients, (2) a multicenter study design, (3) stringent exclusion criteria that enhanced the robustness of our patient selection, and (4) the clinical applicability of our results.

5. Conclusion

In summary, our study supports the utility of NLR as a prognostic biomarker in acute ischemic stroke, highlighting its association with inflammatory processes that drive poor patient outcomes. By incorporating NLR measurements into clinical practice, healthcare professionals may enhance their ability to predict stroke recovery trajectories, identify at-risk patients, and implement personalized therapeutic strategies. As we continue to deepen our understanding of the inflammatory mechanisms at play in stroke pathology, further investigations into the role of NLR and other inflammatory markers may pave the way for innovative approaches to improve patient care and outcomes in acute ischemic stroke management.

CRediT authorship contribution statement

Gabriele Prandin: Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mariarosaria Valente:** Writing – review & editing, Visualization. **Liqun Zhang:** Writing – review & editing, Visualization. **EdoardoPirera:** Writing – review & editing, Visualization, Methodology. **Paresh Malhotra:** Writing – review & editing, Visualization. **Simona Sacco:** Writing – review & editing, Visualization. **Matteo Foschi:** Writing – review & editing, Visualization, Methodology. **Raffaele Ornello:** Writing – review & editing. **Viva Levee:** Writing – review & editing. **Katherine Chulack:** Writing – review & editing. **Fahad Sheikh:** Writing – review & editing. **Feras Fayez:** Writing – review & editing. **Francesco Toraldo:** Writing – review & editing. **Domenico Maisano:** Writing – review & editing. **Caterina Del Regno:** Writing – review & editing. **Filippo Komauli:** Writing – review & editing. **Adelaida Gartner Jarmillo:** Writing – review & editing. **Hakam Al-Karadsheh:** Writing – review & editing. **Hamza Zahid:** Writing – review & editing. **Piers Klein:** Writing – review & editing, Visualization. **Mohamad Abdalkader:** Writing – review & editing. **Paolo Manganotti:** Writing – review & editing, Visualization, Conceptualization. **Kyriakos Lobotesis:** Writing – review & editing, Visualization. **Thanh N. Nguyen:** Writing – review & editing, Visualization. **Soma Banerjee:** Writing – review & editing, Visualization. **Gian Luigi Gigli:** Writing – review & editing. **Giovanni Merlino:** Writing – review & editing, Visualization. **Lucio D'Anna:** Writing – original draft, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Informed consent

Informed consent was not a legal requirement as the research was carried out using data collected as part of routine care and any researchers outside the direct care team only had access to anonymized data.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethical approval

This study has obtained approval from the UK Health Regulator Authority (HRA) (HRA Reference No.: 275260). The study has also

received confirmation of capacity and capability from the Imperial College Healthcare NHS Trust.

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None.

Declaration of Competing interest

SB is a key opinion leader for RAPIDAI. All other authors have no conflicts of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2025.123587.

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