Role of Neutrophil-Lymphocyte Ratio in the Prognosis of Acute Ischaemic Stroke After Reperfusion Therapy: A Systematic Review and Meta-analysis

Divyansh Sharma[1,2], Kevin J. Spring[2,3,4] and
Sonu M. M. Bhaskar[1,2,3,5] ⓘ

[1]Global Health Neurology and Translational Neuroscience Laboratory, Sydney and Neurovascular
Imaging Laboratory, Clinical Sciences Stream, Ingham Institute for Applied Medical Research, Sydney,
NSW, Australia. [2]South-Western Sydney Clinical School, University of New South Wales (UNSW),
Sydney, NSW, Australia. [3]NSW Brain Clot Bank, NSW Health Pathology, Sydney, NSW, Australia.
[4]Medical Oncology Group, Liverpool Clinical School, Western Sydney University and Ingham Institute of
Applied Medical Research, Sydney, NSW, Australia. [5]Department of Neurology & Neurophysiology,
Liverpool Hospital and South-Western Sydney Local Health District, Comprehensive Stroke Center,
Sydney, NSW, Australia.

ABSTRACT

BACKGROUND: Inflammation may mediate response to acute reperfusion therapy (RT) in acute cerebral ischaemia. Neutrophil-lymphocyte ratio (NLR), an inflammatory biomarker, may play an important role in acute ischaemic stroke (AIS) prognostication.

OBJECTIVE: This meta-analysis sought to examine the effect of NLR on functional outcomes, mortality and adverse outcomes in AIS patients receiving RT.

METHODS: Individual studies were retrieved from PubMed/Medline, EMBASE and Cochrane databases. Data were extracted using a standardised data sheet and meta-analysis on association of admission (pre-RT) or delayed (post-RT) NLR with clinical/safety outcomes after RT was conducted.

RESULTS: Thirty-five studies (n = 10 308) were identified for the systematic review with 27 (n = 8537) included in the meta-analyses. Lower admission NLR was associated with good functional outcomes (GFOs), defined as 3-month modified Rankin scale (mRS) 0–2 (SMD = −.46; 95% CI = −.62 to −.29; P < .0001), mRS 0–1 (SMD = −.44; 95% CI = −.66 to −.22; P < .0001) and early neurological improvement (ENI) (SMD = −.55; 95 % CI = −.84 to −.25; P < .0001). Lower delayed admission NLR was also associated with GFOs (SMD = −.80; 95%CI = −.91 to −.68; P < .0001). Higher admission NLR was significantly associated with mortality (SMD = .49; 95%CI = .12 to .85; P = .009), intracerebral haemorrhage (ICH) (SMD = .34; 95% CI = .09 to .59; P = .007), symptomatic ICH (sICH) (SMD = .48; 95% CI = .07 to .90; P = .022) and stroke-associated infection or pneumonia (SMD = .85; 95% CI = .50, 1.19; P < .0001). Higher delayed NLR was significantly associated with sICH (SMD = 1.40; 95% CI = .60 to 2.19; P = .001), ICH (SMD = .94; 95% CI = .41 to 1.46; P < .0001) and mortality (SMD = 1.12; 95% CI = .57 to 1.67; P < .0001). There were variations in outcomes across RT groups.

CONCLUSION: Higher admission or delayed NLR is significantly associated with worse morbidity, mortality and safety outcomes in AIS patients receiving RT.

KEYWORDS: Stroke, endovascular therapy, meta-analysis, neutrophil-to-lymphocyte ratio, overall survival, prognosis, systematic review, re-perfusion therapy, intravenous thrombolysis

Introduction

Stroke is a leading cause of death and disease,[1,2] and identifying prognostic biomarkers for this is of great clinical interest.[3-6] Acute Ischaemic Stroke (AIS) forms the vast majority of strokes and occurs when blood flow within the brain is obstructed, with subsequent parenchymal hypoperfusion leading to a central infarct core and surrounding salvageable penumbra.[7] Recently, 2 reperfusion therapies (RT) have revolutionised AIS management and outcomes: Intravenous thrombolysis (IVT) and endovascular therapy (EVT).[8] Acute RT reduce conversion of

penumbral tissue to core infarct by restoring blood flow.[9] Specifically, IVT shows benefit when administered within 4.5 hours of symptom onset, and EVT up to 24 hours.[10-13] There is an increasing understanding of the role of immune-inflammatory system in AIS pathogenesis and RT response, as we have outlined previously.[14] Briefly, acute ischaemia causes blood-brain barrier (BBB) damage, allowing peripheral blood cell entry. Neutrophils are the first peripheral blood cells to enter the brain, within 1 hour, increasing tissue and BBB damage, which potentiates further peripheral cell entry.[15-19] Lymphocytes generally enter 1–2 days post-AIS and are also thought to have a net deleterious effect[14,16,20] Both these cells interact bidirectionally with resident brain immune cells to further mediate AIS damage.[21-23] Neutrophils mediate this by aggravating thrombus formation and preventing the restoration of blood flow,[16,19,20] but the role of lymphocytes is still unclear in the setting of AIS following RT.[14,24]

Blood-based biomarkers such as neutrophil-lymphocyte ratio (NLR) have been implicated in the ongoing management and prognosis of patients in the emergency medicine context,[25-27] patients with acute and chronic coronary syndromes, including those receiving RT,[28-31] and specifically in AIS.[14] Previous studies have demonstrated the utility of NLR in predicting AIS-related morbidity and mortality,[32-34] angiographic outcomes,[35,36] symptomatic intracerebral haemorrhage (sICH),[37-39] and intracerebral haemorrhage (ICH).[40] However, the level of association of NLR with clinical outcomes in AIS patients receiving RT is yet to be clearly determined, with previous primary studies limited by small sample sizes and meta-analyses limited by combination of various blood collection timepoints and thresholds.[34,37,38,40-42] For translation of NLR into a routine prognostic biomarker, further validation is warranted before its clinical utility can be fully established. This study sought to investigate the association of NLR, at admission and delayed timepoints, with clinical outcomes in patients receiving RT, by performing a systematic review and meta-analysis.

Our underlying research questions are:

1. Are admission and delayed NLR associated with long-term functional outcomes?

2. Are admission and delayed NLR associated with successful recanalization?

3. Are admission and delayed NLR associated with short-term functional outcomes?

4. Are admission and delayed NLR associated with safety outcomes?

5. Are admission and delayed NLR associated with stroke-associated infection (SAI) or stroke-associated pneumonia (SAP)?

We hypothesise that in RT-treated AIS patients, due to the deleterious impacts of neutrophils and lymphocytes, lower admission and delayed NLR may be associated with more favourable outcomes.

Methods

The study was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[43] (Figure 1), Standards for Reporting Diagnostic Accuracy (STARD)-2015[44] (Supplemental Table 3) and Meta-analysis of Observational Studies in Epidemiology (MOOSE)[45] guidelines (Supplemental Table 4).

Literature Search: Identification and Selection of Studies

Published studies were retrieved from the following databases: Embase, PubMed/Medline and Cochrane Library until 6th July 2021, with no limits imposed upon the starting period. Keywords used in the search included terms or a combination of terms including: 'acute stroke', 'cerebrovascular accident', 'brain ischemia', 'reperfusion', 'endovascular therapy', 'thrombectomy', 'thrombolysis', 'NLR' and 'neutrophil-lymphocyte ratio'. Full search strategies are provided in the Supplementary Information **(Search Strategy),** with a complete list of keywords displayed here. Search strategies were homogenised, with 'mesh' and 'explode' functions used to encompass some terms where relevant in each database. In addition, references of related articles were also examined to retrieve studies relevant to our analysis.

Inclusion and Exclusion Criteria

Studies were eligible if they met the following criteria: (1) patients aged 18 or above; (2) patients diagnosed with AIS, (3) patients receiving RT; (4) studies with good methodological design (including sufficient sample size, determined to be > 20 patients in each group, and presence of a control population). The exclusion criteria were: (1) animal/preclinical studies; (2) duplicated publications; (3) where multiple studies from overlapping centres with varying study periods reporting similar outcomes were present, studies with smaller sample size or shorter study period were rejected; (4) full-text article not available; (5) systematic reviews, conference abstracts, meta-analyses, letters and case reports or series; and (6) studies presented in abstract form, with relevant data on NLR or control group not available or associated outcomes not reported.

Data Extraction

The title and abstracts were first reviewed using Endnote to rule out articles mismatched to the eligibility criteria. The remaining articles were examined thoroughly to determine whether they should be included for the systematic review or meta-analysis according to the eligibility criteria. Reviews, former meta-analyses and opinions were kept separately for further discussion in the manuscript. The screening was conducted independently by 2 authors. Disagreements were discussed and
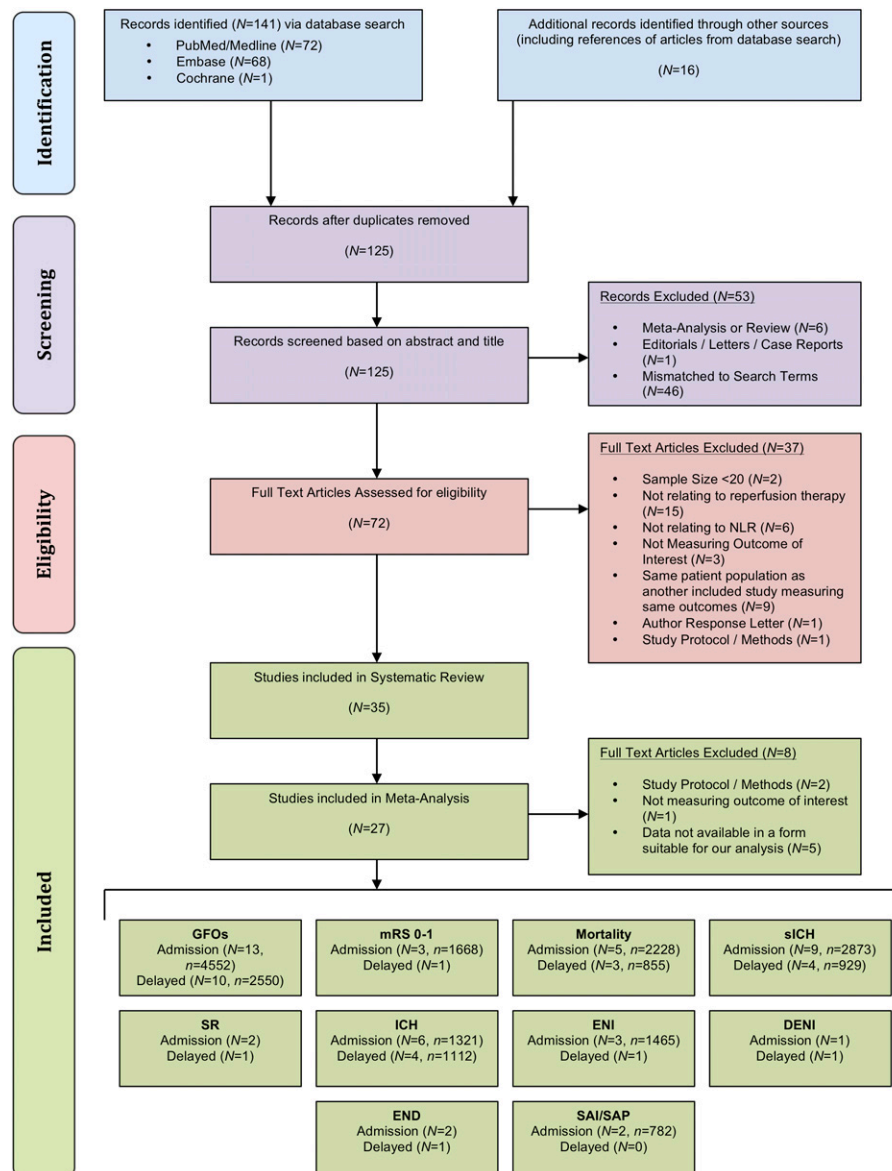
Figure 1. Flow chart of study selection according to the PRISMA diagram. The PRISMA flowchart shows the main characteristics of the included studies. Outcomes for which a meta-analysis could successfully be carried out also have the number of patients shown. Abbreviations: N = Number of Included Studies; n = number of patients; GFOs = Good Functional Outcomes; mRS = Modified Rankin Scale; sICH = Symptomatic intracerebral haemorrhage; SR = Successful Recanalization; ICH = Intracerebral haemorrhage; ENI = Early Neurological Improvement; DENI = Dramatic Early Neurological Improvement; END = Early Neurological Deterioration; SAI = Stroke Associated Infection; SAP = Stroke Associated Pneumonia.

consulted until a consensus was made. Data from each study/ trial was extracted independently using a standardised data extraction sheet to obtain the following information on: (1) baseline demographics: author, country and year of publication; (2) study population: age of patients, sample size, characteristics of AIS patients and RT type; (3) Neutrophil, Lymphocyte Count, NLR; (4) time of collection: admission (pre-intervention) and delayed (post-intervention); (5) outcome measures: primary outcome and secondary outcomes; functional outcomes, mortality, angiographic outcomes and diagnosis; and (6) adverse effects/safety outcomes. NLR was defined as either admission (pre-intervention) or delayed (post-intervention), with the timepoint closest to 24 hours selected for the latter

in the case of multiple values. The primary outcome was defined in terms of morbidity: long-term functional outcomes (defined as good functional outcomes (GFOs) for modified Rankin scale (mRS) score of 0–2, and excellent outcome for mRS score of 0–1) and mortality at 3 months. Prognosis of good and excellent outcomes may be useful for decision-making and hence we included data on both these outcome variables as and when they were available. Short-term functional outcomes were: early neurological improvement (ENI) and dramatic ENI (DENI), defined as improvement in National Institutes of Health Stroke Scale (NIHSS) score[46] by 4 and 8 points respectively, across all studies, or complete recovery or drop to NIHSS 0 or 1, the latter varying between studies, as well as early neurological

deterioration (END), conversely defined as NIHSS score worsening across all studies, with this being by 4 points across most studies. Successful recanalization (SR) was defined as mTICI ≥ 2b across all included studies. Considering safety outcomes, across all studies sICH was determined by neurological decline along with imaging confirmation, and ICH as any radiological evidence of bleeding, with individual variations in study definitions summarised in Supplemental Table 5.

Quality Assessment of Included Studies

The methodological quality of each study was assessed independently by 2 researchers using the modified Jadad scale.[47,48] The scale evaluates study quality based on the following evaluation criteria: randomisation, blinding, withdrawals, dropouts, inclusion/exclusion criteria, adverse effects and statistical analysis. The total score for each study ranged from 0 to 8 points and using the 8 items, the trials/studies were divided into 2 levels. Trials/studies were considered of low quality if they achieved 0–3 points, and of high quality if they achieved 4–8 points. A double-blind got a score of 1 and single-blind .5.

The risk of funding bias in included studies was evaluated independently from the quality assessment through the declaration of funding sources and conflicts of interest using the scoring test developed by Saunders et al. (2017).[49] A score of 1–2 was considered to indicate a moderate potential for bias. The absence of industry funding was not taken to signify an absence of bias, but the presence of industry funding or conflicts of interest was assumed to be an indicator of bias.

Statistical Analysis

All statistical analyses were performed using STATA (Version 13.0, StataCorp LLC, College Station, Texas, USA). Forest plots were generated to present the standardised mean difference (SMD), 95% confidence intervals (CI), percentage weight and heterogeneity between studies included in the meta-analysis. Meta-analyses were split by admission NLR (pre-intervention) and delayed NLR (post-intervention). In cases where there were multiple delayed NLR timepoints, the timepoint closest to 24 hours was taken (Table 2). The I^2 statistics and *P*-values were used to assess heterogeneity between studies, with <40%, 30–60%, 50–90% and 75–100% representing low, moderate, substantial and considerable heterogeneity, respectively.[50] A fixed-effects model was used for heterogeneity <50%, and random-effects model used for heterogeneity > 50%, across all subgroup analyses, with subgroup analyses performed for patients based on which was the primary treatment method, and which was the adjunct: IVT ± EVT, and EVT ± IVT. Where there was only IVT used, this is indicated on the forest plot. Baseline characteristics of patient populations were synthesised from all included studies. Where applicable, median and interquartile ranges were converted to mean and standard deviation using the method described by Wan et al.

(2012), median and ranges were converted to mean and standard deviation using the methods described by Luo et al. (2018)[51] and Wan et al. (2014),[52] respectively, and for studies where SD was not available the method proposed by Walter and Yao (2007) was used to calculate SD, assuming the data was normally distributed.[53] Combined means were calculated where applicable. Where graphical representations of results were provided, numerical values were retrieved by 2 researchers independently. A (Begg's) funnel plot was used to visually detect the presence of publication bias in the meta-analysis. Asymmetry on either side of the funnel plot is indicative of the presence of publication bias. This was also confirmed using Egger's test of effect sizes for publication bias. Where possible, the command 'metainf' was used in STATA to determine the impact of individual studies on the overall meta-analysis (Supplemental Figure 1). P-values < .05 were considered statistically significant.

Results

Description of Included Studies

Twenty-seven studies, with the total number of patients (n) being 8537, were included in the meta-analysis. An additional 8 studies (n = 1771) were included in the systematic review. The mean age was 67.73 ± 13.51 years. There was a slight male preponderance (59.90%) and mean baseline NIHSS was 11.84 ± 7.84. Further patient clinical characteristics, details about outcomes in all studies, and NLR values stratified by outcome are provided in Tables 1, 2 and 3, respectively. Results of methodological quality and funding bias assessment are provided in Supplemental Table 1. A full summary of the results of all meta-analyses are provided in Supplemental Tables 6 and 7.

Association of NLR With 90-day GFOs

There were 13 studies looking at admission NLR (pre-intervention), involving 4552 patients, and 10 studies reporting delayed NLR (post-intervention), comprising of 2550 patients.

Admission NLR with 90-day GFOs. The meta-analysis demonstrated significantly lower admission NLR in patients with GFOs (mRS 0–2) in comparison to those with poor functional outcomes (mRS 3–6) (SMD = −.46; 95% CI = −.62 to −.29; P < .0001; Figure 2). This significant effect was seen in both IVT ± EVT (SMD = −.41; 95% CI = −.62 to −.20; P < .0001) and EVT ± IVT patients (SMD = −.50; 95% CI = −.76 to −.23; P < .0001). There was non-significant heterogeneity between groups (P = .604), but substantial to considerable overall heterogeneity (I^2 = 84.8%, P < .0001). No evidence of publication bias was observed by visual inspection of the funnel plot (Figure 5), and this was confirmed by the Egger's test (Supplemental Table 2 & Supplemental Figure 2). The meta-analysis was repeated with further stratification of the IVT ± EVT group (Figure 2) into IVT only (SMD = −.28; 95% CI = −.50 to

Table 1. Overall summary of baseline clinical characteristics.

CHARACTERISTICS	NUMBER OF PATIENTS FOR WHOM DATA WAS AVAILABLE	NUMBER OF PATIENTS	% OR MEAN (±SD)
Age (Yrs)	9958	N/A	67.73 ± 13.51
Male gender	9741	5835	59.90
Baseline NIHSS	9768	N/A	11.84 ± 7.84
Baseline NLR	7977		4.45 ± 4.02
Delayed NLR	2836		5.31 ± 4.15
BSBP	7513		150.13 ± 24.43
Etiology			
LAA	5481	1982	36.16
CE	5481	1942	35.43
SVO	3652	665	18.67
Other and/or undetermined	5481 (as reported) 3652 (excluding studies not providing SVO data)	808 (as reported) 477 (excluding studies not providing SVO data)	14.74 (as reported) 13.39 (excluding studies not providing SVO data)
Risk factors			
CAD	5427	1056	19.46
AF	9385	2685	28.32
HTN	9625	6380	66.29
DM	9625	2259	23.47
HL/DL	5777	2128	36.84
Smoking	6334	2135	33.71
PS/TIA	8293	1465	17.67

Abbreviations:LAA = Large Artery Atherosclerosis; CE = Cardioembolic; SVO = Small Vessel Occlusion; CAD = Coronary Artery Disease; AF = Atrial Fibrillation; HTN = Hypertension; DM = Diabetes Mellitus; HL = Hyperlipidemia; DL = Dislipidemia; PS = Previous Stroke; TIA = Transient Ischaemic Event; BSBP = Baseline Systolic Blood Pressure; N/A = Not applicable.

−.06; P = .011) and IVT ± EVT (SMD = −.62; 95% CI = −.74 to −.49; P < .0001) studies. There was significant heterogeneity between groups (P = .035).

Delayed NLR with 90-day GFOs. The meta-analysis demonstrated significantly decreased NLR values, collected at delayed timepoints, in patients with 90-day GFOs (SMD = −.80; 95% CI = −.91 to −.68; P < .0001). All patients in the IVT ± EVT group received IVT only, and the forest plot reflected this (Figure 2). The significant effect was seen in patients receiving IVT only (SMD = −.87; 95% CI = −1.03 to −.71; P < .0001), EVT ± IVT (SMD = −.74; 95% CI = −.89 to −.59; P < .0001) and 1 study that had all treatment combinations (SMD = −.59; 95% CI = −.81 to −.36; P < .0001). There was a non-significant heterogeneity between groups (P = .119), and moderate overall heterogeneity (I^2 = 48.7%, P = .041). No major evidence of publication bias was observed by visual inspection of the funnel plot (Figure 5), and this was confirmed by the Egger's test (Supplemental Table 2 & Supplemental Figure 2).

Association of NLR With 90-day mRS 0–1

Considering mRS 0–1, there were 3 studies looking at admission NLR (pre-intervention), with 1668 patients, and only 1

study reporting delayed NLR with 165 patients; a meta-analysis could not be performed for the latter.

Admission NLR with 90-day mRS 0–1. The meta-analysis demonstrated that patients with 90-day excellent outcomes (mRS 0–1) had significantly lower admission NLR relative to those without (mRS 2–6) (SMD = −.44; 95% CI = −.66 to −.22; P < .0001; Figure 2). All studies contained patients receiving IVT ± EVT. There was substantial to considerable heterogeneity between studies (I^2 = 75.0%, P = .018). No evidence of publication bias was observed from visual inspection of the funnel plot (Figure 5), and this was confirmed by the Egger's test (Supplemental Table 2 & Supplemental Figure 2).

Delayed NLR with 90-day mRS 0–1. Only Topcuoglu et al.[54] provided relevant data, reporting that NLR was statistically significantly lower in the mRS 0–1 group.

Association of NLR With 90-day Mortality

There were 5 studies looking at admission NLR (prior to intervention), with 2228 patients, and 3 studies reporting delayed NLR with 855 patients.

Table 2. Clinical characteristics and outcomes of studies included in the meta-analysis.

ID	AUTHOR	YEAR	STUDY TYPE	COUNTRY	REPERFUSION	COHORT SIZE	NLR BLOOD COLLECTION TIME-POINT	NLR (MEAN, SD)	OUTCOME PROPORTIONS (N (%))									
									ENI	DENI	END	GFOS	MRS 0-1	MORTALITY	SICH	ICH	SR	SAI/SAP
1	Aly et al.[56]	2020	Retrospective	NS	EVT ± IVT	142	Admission	3.37 (2.47)				63 (44.37)		35 (24.65)	15 (10.56)		127 (89.44)	
							3–7 days after EVT	5.93 (4.04)										
2*	Brooks et al.[74]	2014	Retrospective	USA	EVT ± IVT	116	Admission	4.30 (3.37)										
3	Chen, He et al.[59]	2021	Retrospective	China	EVT ± IVT	257	Admission	6.04 (5.32)			77 (22.96)	86 (33.46)			22 (8.56)	97 (37.74)	200 (77.82)	
4	Chen, Ren et al.[81]	2021	Retrospective	China	IVT	280	24 hours	3.48 (2.09)				194 (69.28)		27 (9.64)	6 (2.14)			
5	Cheng et al.[82]	2020	Prospective	China	IVT	381	Within 24 hours of admission	4.41 (3.07)			103 (27.03)	226 (59.32)		52 (13.65)				
6*	Duan et al.[35]	2017	Retrospective	China	EVT ± IVT	616	Before EVT					267 (43.34)		153 (24.84)	98 (15.91)	292 (47.40)	509 (82.62)	174 (28.25)
7	Guo et al.[83]	2016	Prospective	China	IVT ± EVT	189	Admission	2.89 (1.60)							17 (8.99)	28 (14.81)		
							3–6 hours after IVT	5.22 (2.68)										
							12–18 hours after IVT	7.54 (4.70)										
							36–48 hours after IVT	7.38 (4.98)										
8	Hu et al.[84]	2021	Retrospective	China	IVT	183	Within 24 hours of IVT	3.8 (2.2)				113 (61.75)		3 (1.64)	5 (2.73)			
9	Li et al.[85]	2021	Retrospective	China	EVT ± IVT	286	Before EVT	4.43 (2.44)				148 (51.75)		36 (12.59)	18 (6.29)	61 (21.33)	269 (94.06)	
10*	Liu, Lu et al.[76]	2020	Prospective	China	IVT	285	Before IVT	2.93 (1.86)							3 (1.05)	72 (25.26)		
11*	Liu, Wu et al.[86]	2020	Retrospective	China	IVT	192	Before IVT	2.97 (1.42)				158 (82.29)				30 (15.63)		
12	Lv et al.[87]	2020	Retrospective	China	IVT	564	Admission	3.37 (2.33)				360 (63.83)						
13	Maestrini et al.[32]	2015	Retrospective	France & Finland	IVT ± EVT	846	Before IVT	3.59 (2.88)				486 (57.45)	363 (42.91)	101 (11.94)	54 (6.38)			
14	Malhotra et al.[33]	2018	Retrospective	USA	IVT ± EVT	657	Before IVT	2.6 (1.63)				452 (68.80)	348 (52.97)	56 (8.52)	21 (3.19)			
15*	Meng et al.[77]	2020	Prospective	China	EVT ± IVT	302	Admission	9.42 (7.90)				118 (39.07)		62 (20.53)	100 (33.11)		265 (87.7)	
16	Oh et al.[88]	2020	Retrospective	NS	EVT ± IVT	411	Admission	5.49 (3.97)				212 (51.58)		37 (9.00)	28 (6.81)	103 (25.06)	382 (92.94)	
17	Oren et al.[89]	2021	Retrospective	Turkey	IVT	133	Admission	2.93 (2.11)							22 (16.79)			

(Continued)

Table 2. Continued.

ID	AUTHOR	YEAR	STUDY TYPE	COUNTRY	REPERFUSION	COHORT SIZE	NLR BLOOD COLLECTION TIME-POINT	NLR (MEAN, SD)	OUTCOME PROPORTIONS (N (%))									
									ENI	DENI	END	GFOS	MRS 0–1	MORTALITY	SICH	ICH	SR	SAI/SAP
18	Ozgen et al.[90]	2020	Retrospective	Turkey	EVT ± IVT	150	Admission	6.47 (4.95)				58 (38.7)		33 (22)			122** (81.3)	
19	Pagram et al.[78]	2016	Retrospective	Australia	IVT	141##	Admission	4.20 (1.87)				82 (58.16)						
							Within 24 hours of IVT	7.03 (4.51)										
20	Pikija et al.[79]	2018	Retrospective	Austria	EVT ± IVT	187	Admission	3.83 (2.76)				90 (48.13)		37 (19.79)	13 (6.95)	31 (16.58)	141 (75.40)	
21	Semerano et al.[71]	2019	Retrospective	Spain	EVT ± IVT	433	3 hours before EVT	3.65 (2.83)				242 (55.89)		106 (24.48)	65 (15.01)	197 (45.50)	345 (79.68)	
							Day 1 after EVT	6.06 (3.83)										
22	Sengeze et al.[36]	2020	Retrospective	Turkey	EVT ± IVT	84	Admission	5.75 (4.96)				25 (29.76)		31 (36.90)			39 (46.43)	
23	Shi, Peng et al.[73]	2018	Retrospective	China	IVT	372	Before IVT	3.26 (2.87)				245 (65.86)			11 (2.96)	39 (10.48)		
							24 hours after IVT	4.38 (2.78)										
24	Shi, Guo et al.[91]	2021	Retrospective	China	EVT ± IVT	127	Baseline	6.26 (4.54)				69 (54.33)			14 (11.02)			
							Post-operation	8.68 (4.96)										
25	Switonska et al.[58]	2020	Retrospective	Poland	All	51	Admission	6.01 (4.38)							10 (19.61)		21*** (91.30)	
26	Tian et al.[80]	2018	Retrospective	China	IVT	240	Admission	3.37 (3.06)	86 (35.83)									
27	Topcuoglu et al.[54]	2020	Retrospective	Turkey	IVT	165	Before IVT	3.51 (3.63)	86 (52.12)	47 (28.48)		81 (49.09)	54 (32.73)		11 (6.67)	42 (25.45)		
							24 hours after IVT	6.79 (7.75)										
28	Zhu et al.[92]	2020	Retrospective	China	EVT ± IVT	112	Admission	7.83 (5.93)				52 (46.43)		21 (18.75)	8 (7.14)	46 (41.07)	86 (76.79)	81 (72.32)
29	Ferro et al.[62]	2021	Retrospective	Portugal	All	325	After RT, within 24 hours of onset	6.51 (5.23)			85&& (26.15)	147 (45.23)					149 (78.42)	48 (14.80)
30	Feng et al.[93]	2020	Retrospective	China	EVT ± IVT	90	Admission	8.50 (7.91)				43 (47.78)		34 (37.78)			76& (84.44)	
31	Gong et al.[61]	2021	Prospective	China	IVT ± EVT	1060	Admission	4.22 (2.00)	398 (37.55)		193 (18.21)			82 (7.74)				
32	Deng et al.[94]	2020	Prospective	China	IVT	337	Admission	4.98 (3.41)										141 (41.84)
					EVT ± IVT	333	Before EVT	9.00 (6.44)									296 (88.89)	219 (65.77)
33*	Sarioglu et al.[57]	2020	Retrospective	Turkey	EVT ± IVT	83	Admission	4.55 (3.95)				49 (59.04)		13 (15.66)	17 (20.48)		65 (78.31)	

(Continued)

Table 2. Continued.

ID	AUTHOR	YEAR	STUDY TYPE	COUNTRY	REPERFUSION	COHORT SIZE	NLR BLOOD COLLECTION TIME-POINT	NLR (MEAN, SD)	OUTCOME PROPORTIONS (N (%))									
									ENI	DENI	END	GFOS	MRS 0-1	MORTALITY	SICH	ICH	SR	SAI/SAP
34*	Lux et al.[55]	2020	Retrospective	UK	EVT ± IVT	121	Admission	3.76 (6.10)						11 (9.09)	25 (20.66)		90 (74.38)	
						113	24 hours	7.42 (6.69)						9 (7.96)			85 (75.22)	
35*	Inanc & Inanc[60]	2018	Retrospective	Turkey	EVT ± IVT	56	Admission	9.8 (21.45)						23 (41.07)		24 (42.86)	33### (58.93)	

All values provided to 2 decimal places. Where data was not available, this was left blank. Definitions of outcomes were as outlined in text unless specified otherwise. Further detail around individual study definitions of sICH and ICH outcomes are found in Supplementary Table 5.

*Only included in the systematic review.
**Definition not clearly specified.
***Data only available for 23 patients.
#Data only available for 276 patients.
##Value from tables provided.
###Definition via Thrombolysis in Brain Ischemia Scale.
&Definition via eTICI scale.
&&Defined this as any increase in NIHSS score from baseline.

Abbreviations: ENI = Early Neurological Improvement; DENI = Dramatic ENI; END = Early Neurological Decline; GFOs = Good Functional Outcomes; NLR = Neutrophil-Lymphocyte Ratio; sICH = symptomatic intracerebral haemorrhage; SR = Successful Recanalization; SAI = Stroke-Associated Infection; SAP = Stroke-Associated Pneumonia; NS = Not Specified; IVT = Intravenous Thrombolysis; EVT = Endovascular Therapy; USA = United States of America; UK = United Kingdom; IVT = Intravenous Thrombolysis; RT = Reperfusion Therapy.

Table 3. Neutrophil-lymphocyte ratio (NLR) values stratified by outcome.

ID	AUTHOR	NLR TIME-POINT	OUTCOME GROUP	PATIENTS (N)	NLR VALUE (MEAN, SD)	COMPARATOR GROUP	PATIENTS (N)	NLR VALUE (MEAN, SD)
1	Aly et al.[56]	Admission	GFOs	63	3.13 (2.58)	No GFOs	79	3.5 (2.42)
			sICH	15	2.77 (2.04)	No sICH	127	3.47 (2.32)
			Mortality	35	3.23 (2.47)	No mortality	107	3.37 (2.48)
			SR	127	3.47 (2.70)	No SR	15	2.73 (1.47)
		3-7 days after EVT	GFOs	63	4.2 (2.28)	No GFOs	79	7 (5.21)
			sICH	15	8.73 (10.06)	No sICH	127	5.83 (4.05)
			Mortality	35	7.17 (4.95)	No mortality	107	5.13 (3.23)
			SR	127	5.37 (3.52)	No SR	15	8.37 (9.57)
2	Brooks et al.[74]	Admission						
3	Chen, He et al.[59]	Admission	GFOs	86	4.4 (3.39)	No GFOs	171	6.87 (5.91)
			END	77	8.02 (8.26)	No END	180	5 (3.50)
			ICH	97	6.61 (5.53)	No ICH	160	5.26 (4.09)
			sICH	22	9.69 (7.92)	No sICH	235	5.47 (4.08)
4	Chen, Ren et al.[81]	24 hours	GFOs	194	2.92 (1.43)	No GFOs	86	5.24 (3.25)
			Mortality	27	7.13 (5.48)	No mortality	253	3.19 (1.69)
5	Cheng et al.[82]	Within 24 hours of admission	GFOs	226	3.54 (2.07)	No GFOs	155	6.06 (4.22)
6	Duan et al.[35]	Before EVT						
7	Guo et al.[83]	Admission	ICH	28	2.92 (1.84)	No ICH	161	2.88 (1.56)
			sICH	17	2.55 (1.35)	No sICH	172	2.99 (1.58)
		3–6 hours after IVT	ICH	28	7.09 (2.11)	No ICH	161	4.9 (2.64)
			sICH	17	6.71 (2.14)	No sICH	172	5.17 (2.87)
		12–18 hours after IVT	ICH	28	13.90 (4.32)	No ICH	161	6.44 (3.82)
			sICH	17	13.38 (6.93)	No sICH	172	6.99 (4.61)
		36–48 hours after IVT	ICH	28	13.22 (4.25)	No ICH	161	6.36 (4.36)
			sICH	17	12.57 (8.28)	No sICH	172	6.84 (4.43)
8	Hu et al.[84]	Within 24 hours of IVT	GFOs	113	3.30 (1.90)	No GFOs	70	4.60 (2.40)
9	Li et al.[85]	Before EVT	GFOs	148	3.56 (1.50)	No GFOs	138	5.64 (3.29)
10	Liu, Lu et al.[76]	Before IVT						

(Continued)

Table 3. Continued.

ID	AUTHOR	NLR TIME-POINT	OUTCOME GROUP	PATIENTS (N)	NLR VALUE (MEAN, SD)	COMPARATOR GROUP	PATIENTS (N)	NLR VALUE (MEAN, SD)
11	Liu, Wu et al.[86]	Before IVT	GFOs	360	3.29 (2.13)	No GFOs	206	3.59 (2.95)
12	Lv et al.[87]	Admission	mRS 0–1	483	4.37 (3.35)	No mRS 0–1	363	2.70 (1.41)
13	Maestrini et al.[32]	Before IVT	GFOs	486	2.90 (1.64)	No GFOs	360	4.73 (3.72)
			Mortality	101	6.60 (6.39)	No mortality	745	3.33 (2.23)
			sICH	54	6.90 (6.40)	No sICH	792	3.37 (2.30)
14	Malhotra et al.[33]	Before IVT	mRS 0–1	311	2.90 (1.86)	No mRS 0–1	346	2.23 (1.34)
			GFOs	452	2.27 (1.26)	No GFOs	205	3.17 (2.31)
			Mortality	56	3.53 (3.20)	No mortality	601	2.83 (1.56)
			sICH	21	3.13 (2.46)	No sICH	636	2.67 (1.78)
15	Meng et al.[77]	Admission						
16	Oh et al.[88]	Admission	GFOs	212	3.78 (2.86)	No GFOs	199	7.32 (4.18)
17	Oren et al.[89]	Admission	sICH	22	3.21 (2.08)	No sICH	111	2.87 (2.12)
18	Ozgen et al.[90]	Admission	GFOs	58	4.70 (4.61)	No GFOs	92	7.59 (4.86)
			Mortality	33	6.95 (3.13)	No mortality	117	5.04 (4.90)
19	Pagram et al.[78]	Admission	GFOs	82	3.70 (1.40)	No GFOs	59	4.90 (2.20)
		Within 24 hours of IVT	GFOs	82	5.40 (2.50)	No GFOs	59	9.30 (5.60)
20	Pikija et al.[79]	Admission	ICH	31	5.47 (4.27)	No ICH	156	3.43 (2.47)
21	Semerano et al.[71]	3 hours before EVT	ICH	197	3.67 (2.91)	No ICH	236	3.63 (2.76)
			sICH	65	4.03 (3.49)	No sICH	368	3.57 (2.60)
			GFOs	191	3.07 (2.02)	No GFOs	242	4.10 (3.43)
			Mortality	106	4.87 (3.91)	No mortality	327	3.37 (2.53)
		Day 1 after EVT	ICH	197	6.77 (4.56)	No ICH	236	5.47 (2.98)
			sICH	65	8.67 (5.23)	No sICH	368	5.57 (3.05)
			GFOs	191	4.53 (2.47)	No GFOs	242	7.70 (4.85)
			Mortality	106	10.13 (7.74)	No mortality	327	5.13 (2.61)
22	Sengeze et al.[36]	Admission	SR	39	4.39 (3.26)	No SR	45	6.92 (5.85)

(Continued)

Table 3. Continued.

ID	AUTHOR	NLR TIME-POINT	OUTCOME GROUP	PATIENTS (N)	NLR VALUE (MEAN, SD)	COMPARATOR GROUP	PATIENTS (N)	NLR VALUE (MEAN, SD)
23	Shi, Peng et al.[73]	Before IVT	GFOs	245	2.95 (2.03)	No GFOs	127	3.87 (3.96)
		24 hours after IVT	GFOs	245	3.47 (1.94)	No GFOs	127	6.13 (3.27)
24	Shi, Guo et al.[91]	Baseline	GFOs	69	6.31 (4.15)	No GFOs	58	6.24 (5.10)
		Post-operation	GFOs	69	7.15 (3.29)	No GFOs	58	10.53 (7.02)
25	Switonska et al.[58]	Admission	sICH	10	10.79 (6.86)	No sICH	41	5.34 (4.07)
26	Tian et al.[80]	Admission	ENI	86	2.67 (2.04)	No ENI	154	3.93 (4.04)
27	Topcuoglu et al.[54]	Before IVT	mRS 0–1	110	3.70 (3.98)	No mRS 0–1	54	3.10 (2.77)
			GFOs	81	3.31 (3.38)	No GFOs	84	3.69 (3.88)
			ICH	43	4.63 (5.81)	No ICH	122	3.12 (2.36)
			sICH	11	6.94 (7.31)	No sICH	154	3.27 (3.12)
			ENI	86	2.77 (2.20)	No ENI	79	4.32 (4.60)
			DENI	47	2.69 (1.58)	No DENI	118	3.84 (4.14)
		24 hours after IVT	mRS 0–1	110	8.26 (8.94)	No mRS 0–1	54	3.85 (2.52)
			GFOs	81	4.37 (3.38)	No GFOs	84	9.18 (9.80)
			ICH	43	11.66 (12.39)	No ICH	122	5.10 (4.10)
			sICH	11	23.97 (18.26)	No sICH	154	5.58 (4.46)
			ENI	86	4.87 (4.44)	No ENI	79	8.89 (9.82)
			DENI	47	3.79 (2.26)	No DENI	118	7.98 (8.79)
28	Zhu et al.[92]	Admission	SAP	31	6.23 (4.35)	No SAP	81	16.33 (13.44)
29	Ferro et al.[62]	After RT, within 24 hours of onset	GFOs	147	4.97 (4.40)	No GFOs	178	7.92 (5.49)
			END	85	8.43 (6.50)	No END	240	6.05 (4.96)
			ICH	168*	8.36 (5.76)	No ICH	160*	4.85 (4.14)
30	Feng et al.[93]	Admission	ICH	34	11.95 (10.00)	No ICH	56	6.40 (5.42)
31	Gong et al.[61]	Admission	END	193	6.18 (2.68)	No END	867	3.78 (1.50)
			ENI	398	3.31 (1.25)	No ENI	662	4.77 (2.16)
32**	Deng et al.[94]	Before EVT	SAI (EVT ± IVT cohort)	219	10.16 (7.26)	No SAI (EVT ± IVT cohort)	114	6.73 (3.89)
		Admission	SAI (IVT only cohort)	141	6.95 (4.80)	No SAI (IVT only cohort)	196	3.88 (2.17)
33	Sarioglu et al.[57]	Admission	FPE	32	2.96 (1.94)	No FPE	51	5.55 (4.55)

(Continued)

Table 3. Continued.

ID	AUTHOR	NLR TIME-POINT	OUTCOME GROUP	PATIENTS (N)	NLR VALUE (MEAN, SD)	COMPARATOR GROUP	PATIENTS (N)	NLR VALUE (MEAN, SD)
34	Lux et al.[55]	Admission						
		24 hours						
35	Inanc & Inanc[60]	Admission	ICH	24	6.94 (6.56)	No ICH	32	22.63 (38.30)
			Mortality	23	26.81 (41.38)	No mortality	33	6.47 (5.83)

Table providing a summary of NLR values by outcome and comparator groups. All values were provided to 2 decimal places where rounding was required. Outcome groups where data was available included only. Definitions of outcomes were as outlined in text and the caption of Table 2.

*Total patient numbers for this outcome were not consistent with total patient numbers from other outcomes, but considering the very small magnitude of the discrepancy, numbers were used as reported in tables.

**Two differing cohorts (based on reperfusion therapy type) with relevant data were reported, as specified in Table 2, and hence these were reported/considered separately.

Abbreviations: NLR = Neutrophil-Lymphocyte Ratio; n = Number of patients; SD = Standard Deviation; GFOs = Good Functional Outcomes; sICH = Symptomatic Intracerebral Haemorrhage; SR = Successful Recanalization; EVT = Endovascular Therapy; END = Early Neurological Decline; ICH = Intracerebral Haemorrhage; IVT = Intravenous Thrombolysis; mRS = Modified Rankin Scale; ENI = Early Neurological Improvement; DENI = Dramatic ENI; SAP = Stroke-Associated Pneumonia; SAI = Stroke-Associated Infection; FPE = First Pass Effect.
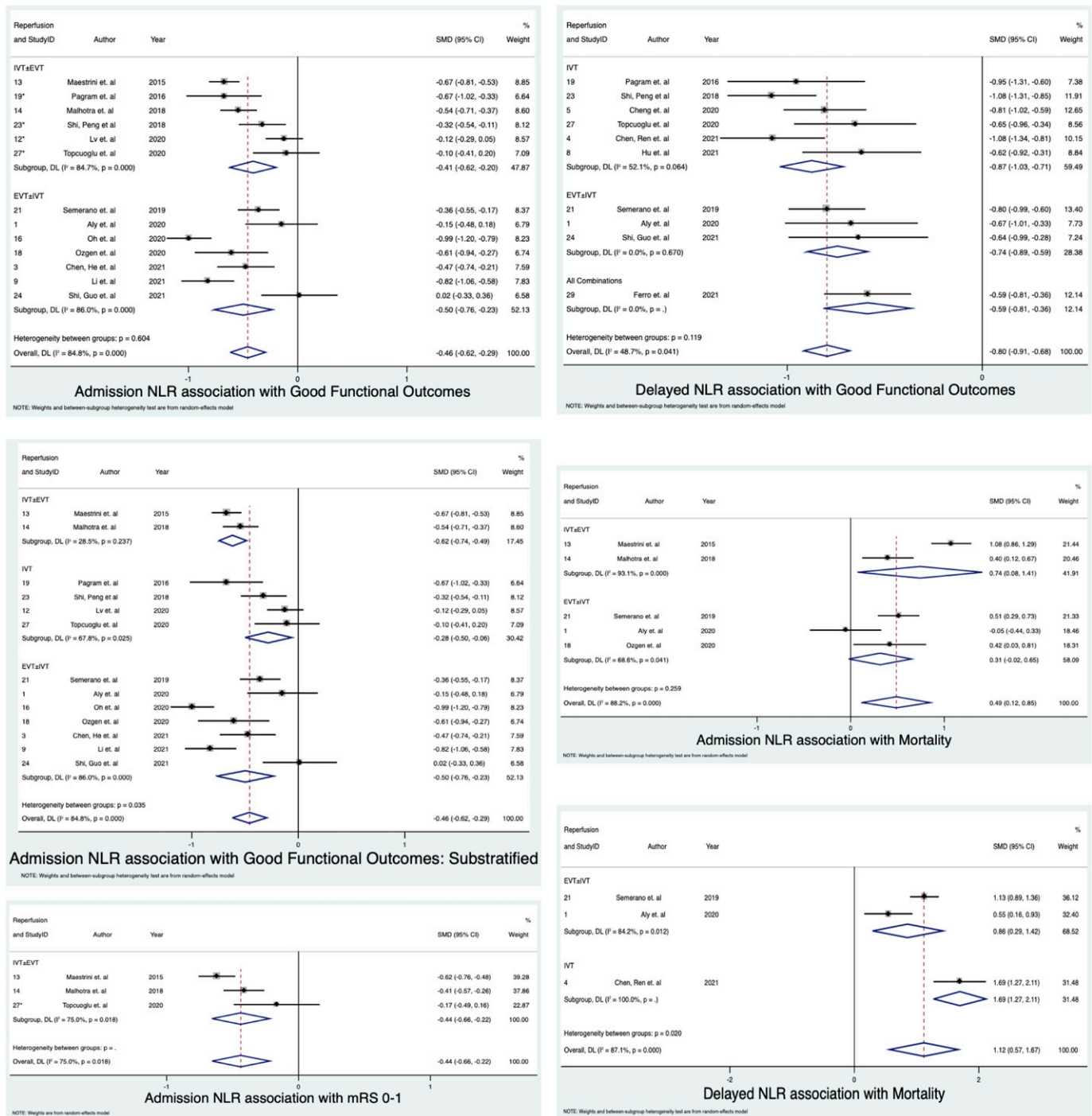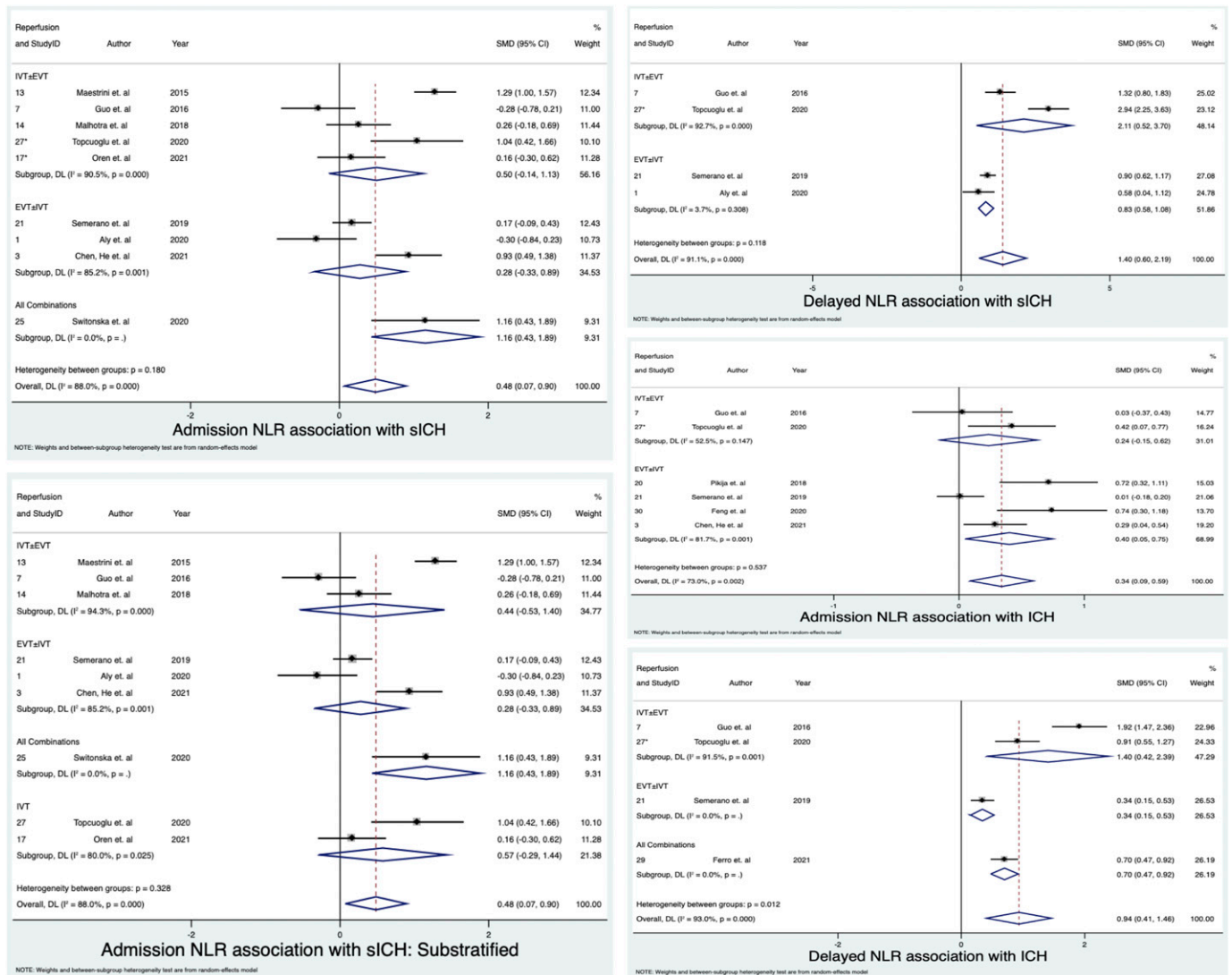
Figure 2. Forest plot of meta-analysis on the association of neutrophil-lymphocyte ratio (NLR) with functional outcomes and mortality at 90 days in acute ischaemic stroke patients receiving reperfusion therapy. Abbreviations: mRS = Modified Rankin Scale; NLR = Neutrophil-Lymphocyte Ratio; IVT = Intravenous Thrombolysis; EVT = Endovascular Thrombectomy. Note: Studies, where only IVT was used with no EVT adjunct, are denoted with an asterisk (*) unless these have been already split up into TPA and IVT ± EVT.

Admission NLR with 90-day mortality. The meta-analysis demonstrated significantly increased admission NLR in patients with 90-day mortality (SMD = .49; 95% CI = .12 to .85; P = .009; Figure 2). This effect was seen in patients receiving IVT ± EVT (SMD = .74; 95% CI = .08 to 1.41; P = .028) but did not reach statistical significance in those receiving EVT ± IVT (SMD = .31; 95% CI = −.02 to .65; P = .067). There was a non-significant heterogeneity between groups (P = .259), but

substantial to considerable overall heterogeneity (I^2 = 88.2%, P < .0001). No evidence of publication bias was observed by visual inspection of the funnel plot (Figure 5), and this was confirmed by the Egger's test (Supplemental Table 2 & Supplemental Figure 2).

Delayed NLR with 90-day mortality. The meta-analysis showed that higher delayed NLR values in patients with 90-day mortality (SMD = 1.12; 95% CI = .57 to 1.67; P < .0001).

Figure 3. Forest plot of meta-analysis on the association of neutrophil-lymphocyte ratio (NLR) with bleeding complication outcomes in acute ischaemic stroke patients receiving reperfusion therapy. Abbreviations: ICH = Intracerebral Hemorrhage; sICH = Symptomatic Intracerebral Hemorrhage; NLR = Neutrophil-Lymphocyte Ratio; IVT = Intravenous Thrombolysis; EVT = Endovascular Thrombectomy. Note: Studies, where only IVT was used with no EVT adjunct, are denoted with an asterisk (*) unless these have been already split up into IVT and IVT ± EVT.

All patients in the IVT ± EVT group received IVT only, and the forest plot reflected this (Figure 2). The significant effect was seen in the 1 study containing patients receiving IVT only (SMD = 1.69; 95% CI = 1.27 to 2.11; P < .0001) and both studies where patients received EVT ± IVT (SMD = .86; 95% CI = .29 to 1.42; P = .003). There was significant heterogeneity between groups (P = .020), and substantial to considerable overall heterogeneity (I^2 = 87.1%, P < .0001). No evidence of publication bias was observed by visual inspection of the funnel plot (Figure 5), and this was confirmed by the Egger's test (Supplemental Table 2 & Supplemental Figure 2).

Association of NLR With SR

Admission NLR grouped according to SR status (SR vs no-SR) was only reported in 2 studies (n = 226), and only 1 study reported delayed NLR (n = 142) grouped as such. Thus, a meta-analysis could not be performed for either due to an insufficient number of studies. For this outcome, 2 studies also considered temporal NLR changes from admission to 24 hours, with mixed results, as Lux et al. reported that these were not significantly associated with SR,[55] but Aly et al. reported statistically significant smaller temporal changes in the SR group.[56]

Admission NLR with SR. The systematic review indicated mixed results, with Aly et al.[56] reporting a higher NLR in the SR group and Sengeze et al.[36] a lower NLR. Differences between groups were statistically significant in both studies. Lux et al. and Duan et al. did not provide groupwise data by outcome but reported conflictingly that admission NLR was not significantly correlated with SR and NLR > 7 was significantly associated with higher SR rates, respectively.[35,55]

Delayed NLR with SR. Again, the systematic review indicated mixed results. Aly et al. reported a statistically significantly higher
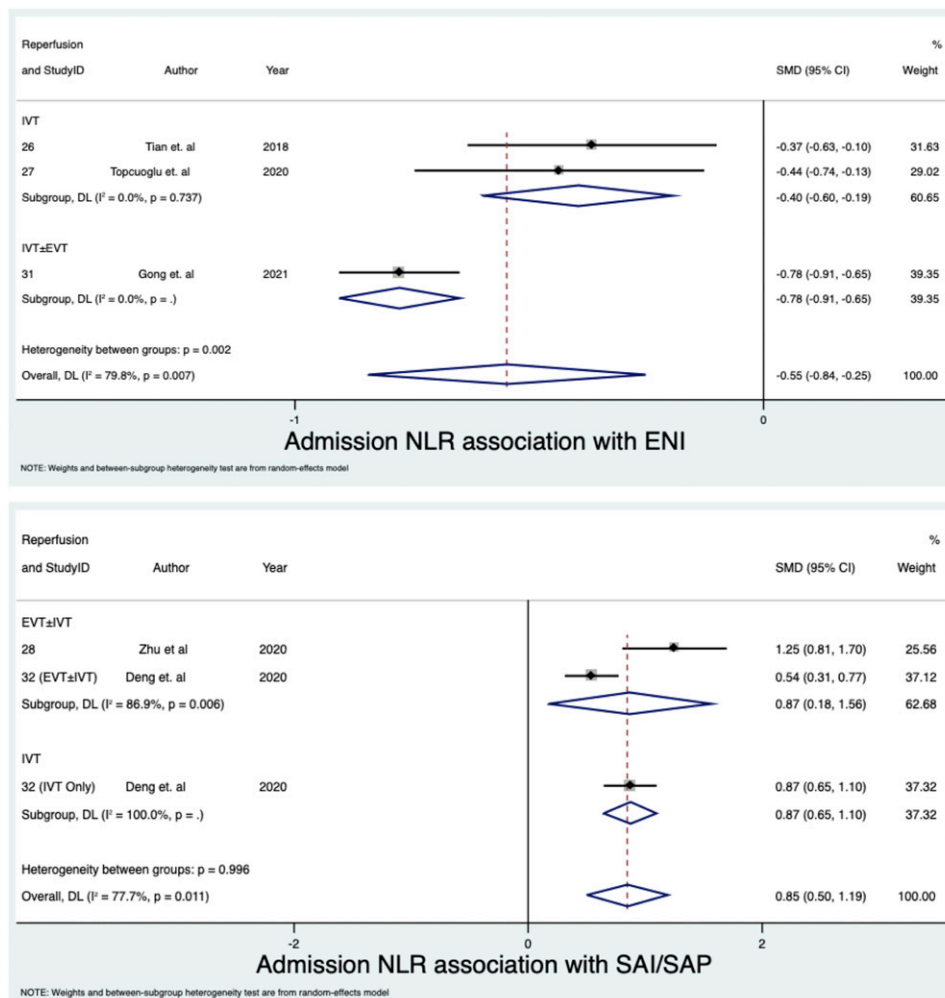
Figure 4. Forest plot of meta-analysis on the association of neutrophil-lymphocyte ratio (NLR) with early neurological improvement and stroke-associated infection outcomes in acute ischaemic stroke patients receiving reperfusion therapy. Abbreviations: ENI = Early Neurological Improvement; SAI = Stroke-Associated Infection; SAP = Stroke-Associated Pneumonia; NLR = Neutrophil-Lymphocyte Ratio; IVT = Intravenous Thrombolysis; EVT = Endovascular Thrombectomy. Note: Studies, where only IVT was used with no EVT adjunct, are denoted with an asterisk (*), unless these have been already split up into IVT and IVT ± EVT.

NLR in the SR group. Lux et al. did not provide groupwise data but reported that admission NLR was not significantly associated with SR.[55] One study also considered the first pass effect (FPE), where complete recanalization (mTICI 3) is achieved with a single pass and reported a lower NLR in the FPE group.[57]

Association of NLR With sICH

There were 9 studies looking at admission NLR (prior to intervention), with 2873 patients, and 4 studies reporting delayed NLR with 929 patients.

Admission NLR with sICH. The meta-analysis revealed higher admission NLR in sICH patients relative to non-sICH (SMD = .48; 95% CI = .07 to .90; P = .022; Figure 3). However, subgroup analyses failed to reach statistical significance in both IVT ± EVT (SMD = .50; 95% CI = −.14 to 1.13; P = .123) and EVT ± IVT groups (SMD = .28; 95% CI = −.33 to .89; P =

.376), with a study where all treatment combinations were reported forming a third group (SMD = 1.16; 95% CI = .43 to 1.89; P = .002). There was a non-significant heterogeneity between studies (P = .180), but substantial to considerable overall heterogeneity (I^2 = 88.0%, P < .0001). Evidence of publication bias was observed by visual inspection of the funnel plot (Figure 5), and this was confirmed by the Egger's test (Supplemental Table 2 & Supplemental Figure 2).

Further stratification of the IVT ± EVT group into IVT only (SMD = .57; 95% CI = −.29 to 1.44; P = .191) and IVT ± EVT (SMD = .44; 95% CI = −.53 to 1.40; P = .376) still yielded statistically insignificant results for each subgroup (Figure 3), and a non-significant heterogeneity between groups (P = .328). Removing the study will all treatment combinations, Switonska et al.,[58] caused statistical significance to be lost (SMD = .41; 95% CI = −.02 to −.85), but this was also observed for the removal of 3 other studies[32,54,59] (Supplemental Figure 1). Inanc & Inanc,[60] included in the systematic review but not
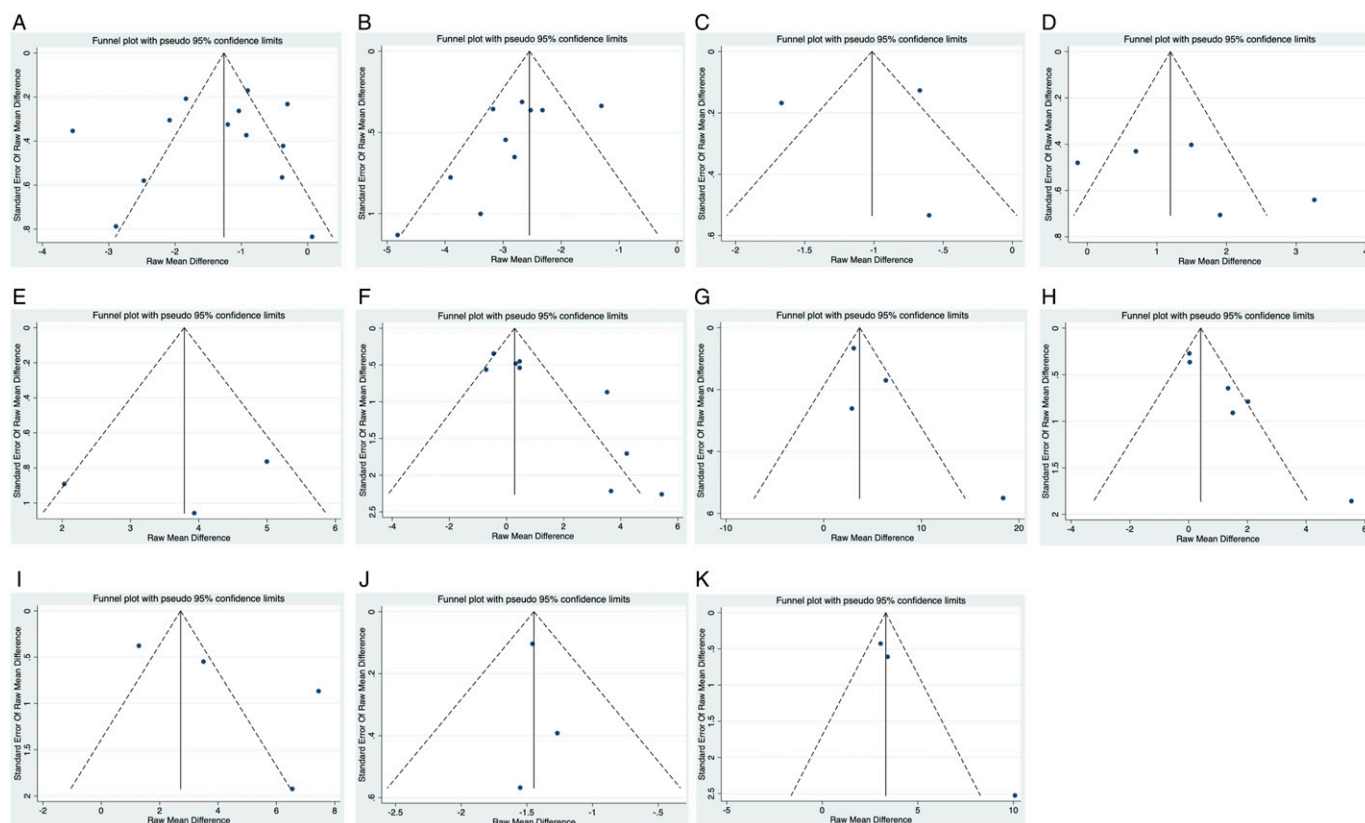
Figure 5. Funnel plots of meta-analyses studies on effect of neutrophil-lymphocyte ratio (NLR) on clinical and safety outcomes in acute ischemic stroke patients receiving reperfusion therapy. A: Admission NLR association with Good Functional Outcomes; B: Delayed NLR association with Good Functional Outcomes; C: Admission NLR association with mRS 0–1; D: Admission NLR association with Mortality; E: Delayed NLR association with Mortality; F: Admission NLR association with sICH; G: Delayed NLR association with sICH; H: Admission NLR association with ICH; I: Delayed NLR association with ICH; J: Admission NLR association with ENI; K: Admission NLR association with stroke-associated infection/pneumonia (SAI)/(SAP). Note: Funnel plots for each meta-analysis.

meta-analysis, also reported an increased NLR in sICH patients as opposed to non-sICH.

Delayed NLR with sICH. The meta-analysis showed significantly higher delayed NLR in sICH patients relative to non-sICH (SMD = 1.40; 95% CI = .60 to 2.19; P = .001 Figure 3). This was seen in both IVT ± EVT (SMD = 2.11; 95% CI = .52 to 3.70; P = .009) and EVT ± IVT treated groups (SMD = .83; 95% CI = .58 to 1.08; P < .0001). There was non-significant heterogeneity between groups (P = .118), but considerable overall heterogeneity (I^2 = 91.1%, P < .0001) was observed. No evidence of publication bias was observed by visual inspection of the funnel plot (Figure 5), and this was confirmed by the Egger's test (Supplemental Table 2 & Supplemental Figure 2). Notably, the overall effect became markedly weaker with the exclusion of Topcuoglu et al. but was still statistically significant (SMD = .93; 95% CI = .57 to 1.27; Supplemental Figure 1).

Association of NLR With ICH

Six studies comprising of 1321 patients reported admission NLR data, whilst 4 studies reported relevant delayed NLR data, in 1112 patients.

Admission NLR with ICH. The meta-analysis demonstrated significantly higher admission NLR in patients with ICH relative to non-ICH (SMD = .34; 95% CI = .09 to .59; P = .007; Figure 3). Patients treated with IVT ± EVT showed no significant effect (SMD = .24; 95% CI = −.15 to .62; P = .229), but a significant effect was observed in EVT ± IVT treated patients (SMD = .40; 95% CI = .05 to .75; P = .024). Non-significant heterogeneity between groups (P = .537), albeit substantial overall heterogeneity (I^2 = 73.0%, P = .004), was observed. Possible publication bias was observed by visual inspection of the funnel plot (Figure 5), and this was supported by Egger's test (Supplemental Table 2 & Supplemental Figure 2).

Delayed NLR with ICH. Significantly increased NLR collected at delayed time points was observed in patients with ICH (SMD = .94; 95% CI = .41 to 1.46; P < .0001; Figure 3). Patients treated with IVT ± EVT showed this significant effect (SMD = 1.40; 95% CI = .42 to 2.39; P = .005), as did EVT ± IVT treated patients (SMD = .34; 95% CI = .15 to .53; P < .0001) and patients for studies where all treatment combinations were used (SMD = .70; 95% CI = .41 to 1.46; P < .0001), albeit with only 1 study included in both these groups. There was significant heterogeneity between groups (P = .012), and

considerable overall heterogeneity (I^2 = 93.0%, P < .0001). Possible publication bias was observed by visual inspection of the funnel plot (Figure 5), but this was not supported by Egger's test (Supplemental Table 2 & Supplemental Figure 2).

Association of NLR With ENI

There were 3 studies reporting admission NLR values with 1465 patients, and one study reporting relevant delayed NLR data, with 165 patients; a meta-analysis could not be carried out for the latter.

Admission NLR with ENI. The meta-analysis showed that patients with ENI have significantly lower admission NLR relative to those without ENI (SMD = −.55; 95% CI = −.84 to −.25; P < .0001; Figure 4). All patients were treated with IVT ± EVT, and hence this was split into IVT only (SMD = −.40; 95% CI = −.60 to −.19; P < .0001) and IVT ± EVT (SMD = −.78; 95% CI = −.91 to −.65; P < .0001) groups, the latter having only 1 study. There was significant heterogeneity between groups (P = .002) and substantial to considerable overall heterogeneity (I^2 = 79.8%, P = .0007). No evidence of publication bias was observed by visual inspection of the funnel plot (Figure 5), and this was supported by Egger's test (Supplemental Table 2 & Supplemental Figure 2). Notably, the omission of Gong et al.[61] caused this effect to weaken (SMD = −.60; 95% CI = −.40 to −.19) most, as compared to the omission of other studies (Supplemental Figure 1).

Delayed NLR with ENI. Only Topcuoglu et al.[54] provided relevant data, reporting that NLR was statistically significantly lower in the ENI group.

Association of NLR With DENI

Only 1 study with 165 patients reported relevant NLR data for this outcome; thus, a meta-analysis was not carried out. However, in this study both admission and delayed NLR were lower in the group with DENI, but this was not statistically significant.[54] Considering the systematic review, Inanc & Inanc looked at correlation between NIHSS scores and median admission NLR[60] was not statistically significant.

Association of NLR With END

Two studies reported admission NLR data, with a total of 1317 patients, and only 1 study for delayed NLR data, with 325 patients.

Admission NLR association with END. The systematic review indicated that higher admission NLR was associated with END, with both studies reporting statistically significant groupwise data reflecting this.[59,61]

Delayed NLR association with END. Only Ferro et al.[62] provided relevant data, reporting a lower NLR in the END group, and a significant association of delayed NLR with END on multivariate analysis.

Association of NLR With SAI And/or SAP

For this meta-analysis, SAI and stroke-associated pneumonia (SAP) were combined. Only admission NLR values were reported, in 2 studies, with 782 patients, although one of these studies reported 2 cohorts based on treatment regimen, and thus a meta-analysis was successfully conducted.

Admission NLR with SAI or SAP. The meta-analysis found significantly higher admission NLR in patients with SAI or SAP (SMD = .85; 95% CI = .50 to 1.19; P < .0001; Figure 4). This significant effect was maintained in EVT ± IVT (SMD = .87; 95% CI = .18, 1.56; P = .014) and IVT only (SMD = .87; 95% CI = .65, 1.10; P < .0001) groups, though the latter contained only 1 study. There was non-significant heterogeneity between the groups (P = .996), but substantial to considerable overall heterogeneity (I^2 = 77.7%, P < .011). No evidence of publication bias was observed by visual inspection of the funnel plot (Figure 5), and this was confirmed by the Egger's test (Supplemental Table 2 & Supplemental Figure 2).

Discussion and Conclusions

This study investigated the association of NLR with clinical and safety outcomes in AIS patients receiving RT. We demonstrate that both admission and delayed NLR are significantly associated with 90-day GFOs (mRS 0–2), and that lower admission NLR is associated with 90-day excellent outcomes (mRS 0–1). Higher admission NLR was significantly associated with SAI or SAP. Notably, we also show that delayed NLR has a larger SMD for GFOs than admission NLR demonstrating better prognostic utility. Increased admission and delayed NLR were both associated with ICH, sICH and mortality. As such, we clearly show that there is a role for NLR in both prognostication and improved clinical safety outcomes, underscoring the clinical implications of NLR in AIS patients receiving RT.

Inflammation is known to play a role in the pathophysiology of AIS, and NLR has been established as a marker for this.[63] This potentially explains our finding that lower admission and delayed NLR is associated with better outcomes and is supported by previous meta-analyses[37,41,42] which demonstrate a predictive role of NLR for predicting clinical outcomes. By imposing more stringent criteria for NLR collection timepoints, we demonstrated that delayed NLR has a larger SMD for GFOs than admission NLR. This could be related to underlying pathophysiology; as lymphocyte entry into ischaemic tissue is thought to occur some 1–2 days after initial cerebral ischaemia,[16] and subsequently causes further pro-inflammatory cytokine release and damage[9,16,19,20]; measuring NLR at this

timepoint may improve prognostication for functional outcomes.[14] This contradicts earlier findings by Song et al.,[34] who reported that admission NLR was better at predicting 3-month mRS outcomes than delayed NLR timepoints. However, our meta-analysis includes more than twice the number of studies, including numerous more recent studies, and we impose a more stringent inclusion criteria, as they also included studies with good functional outcomes defined as mRS 0–1, as well as mRS assessments at times other than 90 days. Additionally, our finding that admission NLR is lower in patients with 90-day GFOs could help stratify patients and guide initial management decisions.[14] Repeating this analysis also showed that NLR SMD was even lower in patients receiving IVT ± EVT than those receiving IVT only. This may have clinical decision-making implications with regards to treatment selection, and shows that there is a role for admission NLR in prognostication for patients receiving adjunct EVT, despite previous authors having hypothesised that EVT may modify outcomes and hence admission NLR would not have predictive value.[55] Our meta-analysis also showed that lower admission NLR was significantly associated with excellent outcome at 3-month (mRS 0–1), with a similar SMD to patients with GFOs, suggesting that NLR may be able to predict both mRS 0–1 and GFOs, and hence could potentially inform treatment stratification and follow-up.

Considering mortality, higher admission NLR was seen in patients with 90-day mortality. This is consistent with previous findings, thought to reflect the more pronounced immune response a higher NLR denotes.[34,37,40] Notably, this effect did not reach statistical significance in EVT ± IVT treated patients, which may be related to the selection cohort of patients eligible for EVT; patients offered EVT may be more likely to benefit from their treatment in comparison to patients receiving IVT, due to the more stringent inclusion criteria for the former.[55] Interestingly, the 3 studies for mortality with a patient cohort receiving EVT ± IVT had higher baseline NIHSS scores than patients treated with IVT ± EVT, which may support the notion that treatment differences may play a role in mortality outcomes. We also showed that delayed NLR was associated with 90-day mortality. As with GFOs, a larger SMD was observed with delayed NLR than admission NLR for 90-day mortality, which may relate to the pathophysiological mechanisms outlined earlier.[14] Infections, a major cause of in-hospital mortality, were also examined as combined SAI or SAP, and we found that higher admission NLR was seen in patients with infections. This could be related to prior exposure to a pathogen such as LPS, or potential concurrent stimulation of other molecules such as matrix metalloproteinases, which may cause increased autoimmune responses, and resultantly raise NLR.[21,64] In the setting of Coronavirus Disease 2019 (COVID-19), there is a particular role for biomarkers in triaging, prognosticating and stratification of treatment in patients with COVID-19, considering reports of increased predisposition to and incidence of AIS, as well as concurrent use of

multiple biomarkers to form more accurate prognostic nomograms.[14,65,66] This could be of particular utility if point-of-care instrumentation incorporating NLR were to be successfully developed during and beyond the pandemic,[14,67] considering the strain on healthcare systems and increasing uptake of telemedicine.[66,68]

Our meta-analysis demonstrated that overall increased admission NLR was significantly higher in sICH patients, but interestingly, this was not true for the subgroup analyses stratified by RT type. The detected publication bias may have played a role in this. The overall effect observed is consistent with the meta-analysis by Zhang et al. (2017) which indicated a prognostic role of NLR for sICH. However, stratification by timepoint and treatment type was not performed unlike our study.[14,38] In contrast, delayed NLR values showed a higher SMD for sICH, and this significant effect was preserved regardless of the treatment administered, though the SMD was larger in the IVT ± EVT group than the EVT ± IVT group. Given that higher NLR is associated with larger infarct volume[69] and IVT can increase sICH risk in large infarcts,[70] there may be a role for NLR in guiding treatment decision-making pertaining to suitability for IVT.[14] Additionally, underlying factors such as patients' collaterals status[71] or a history of coronary artery disease, which may manifest as increased antiplatelet use,[39] may have influenced the results observed, but very few studies reported on this and hence we could not account for these. Both admission and delayed NLR were found to be significantly higher in patients with ICH, although in the former group, there was an evidence of publication bias. Notably in subgroup analyses, EVT ± IVT patients showed both significantly lower admission as well as delayed NLR, but this was not seen in IVT ± EVT patients for the admission NLR group. This differs from previous findings by Zhang et al. (2019), who performed a meta-analysis stratified by RT type similar to our study and found NLR to have significant associations with ICH in patients receiving primary IVT but not EVT.[14,40] This difference may be because we include a greater number of more recent studies and impose stricter criteria for NLR time points. Additionally, the difference between associations of NLR with ICH in IVT ± EVT and EVT ± IVT patients in our study might be related to a potential role of IVT in exacerbating blood-brain barrier (BBB) dysfunction, resulting in delayed (post-intervention) NLR having more prognostic value in patients receiving IVT ± EVT than admission (pre-intervention) NLR.[54] Nonetheless, the role of the detected publication bias cannot be discounted, and hence there is a pressing need for further prospective studies considering admission NLR in IVT ± EVT patients developing ICH.

There is a scarcity of studies focussing on SR outcomes. Our systematic review indicated mixed results and thus further research is necessary given the potential role of neutrophils in no-reflow injury.[14,16] With regards to short-term functional outcomes, we could only carry out a meta-analysis to evaluate the association of admission NLR with ENI, which revealed

significantly lower admission NLR in patients with ENI. There are very few studies linking NLR with other short-term functional outcomes, although all included studies showed prognostic benefit. This could be related to NLR being a marker of inflammation and hence being associated with the degree of immune response and neurological outcomes.[14,20,56,72,73] Resultantly, it is critical that further studies be carried out to ascertain this, as well as the role of temporal NLR variations.

The major strengths of our study are use of SMD to account for the continuous nature of NLR, whereas previous meta-analyses have combined various thresholds without such standardisation.[37,38,41,42] Additionally, we looked at admission and delayed NLR separately, which is poignant due to the pathophysiological considerations owing to delayed entry of lymphocytes and subsequent pro-inflammatory cytokine release.[9,16,19,20] By considering IVT ± EVT and EVT ± IVT treated patients separately, our meta-analysis provided comparison of the utility of NLR in either of these patient groups, which can benefit further prognostication, stratification and treatment selection. Finally, we also incorporated the most recent evidence.

Our work is not without limitations. Most of our included studies were retrospective, and there was resultantly high heterogeneity; we sought to minimise this through random-effects modelling. Additionally, varying NLR timepoints were reported; whilst we attempted to address this by defining admission and delayed NLR using pre- and post-intervention NLR, with the timepoint closest to 24 hours in each study used for the latter, NLR's dynamic profile means there may be some impact on results observed for delayed NLR. Very few studies looked at the dynamic NLR profile and hence this could only be considered in the systematic review pertaining to SR. Some studies failed to exclude patients with underlying or acute inflammatory conditions, which can impact NLR,[32,33,39,60,71,73-80] along with the site of blood procurement, which was not specified in several studies. Racial and ethnic differences in NLR have been reported previously,[34,38,40,79] but data was not available for these, and thus we could not account for these. Our study population was AIS patients receiving RT, and thus, should not be extrapolated beyond this group. A further high quality RCT is recommended to corroborate our findings, with specific attention to standardisation of the timepoints and sites at which blood is collected, and appropriate exclusion of patients with infections or acute or chronic inflammatory conditions.

In conclusion, NLR is an important prognostic biomarker in AIS patients receiving RT. Our meta-analysis shows a role for both admission and delayed NLR in predicting long-term functional outcomes and mortality, especially in patients receiving EVT, and for delayed NLR in predicting bleeding complications (ICH and sICH). Our findings indicate a role of NLR in treatment selection and post-RT prognostication.

Authors' Contributions

SMMB conceived the study, contributed to the planning, draft, and revision of the manuscript; supervision of the student. SMMB encouraged DS to investigate and supervised the findings of this work. SMMB and DS wrote the first draft of this paper. All authors contributed to the revision of the manuscript. All authors approved the final draft of the manuscript.

ORCID iD

Sonu M. M. Bhaskar https://orcid.org/0000-0002-9783-3628

REFERENCES

1. Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. 2020;396(10258):1204-1222. doi:10.1016/s0140-6736(20)30925-9.

2. Roth GA, Mensah GA, Johnson CO, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 study. *J Am Coll Cardiol*. 2020;76(25):2982-3021. doi:10.1016/j.jacc.2020.11.010.

3. Rastogi A, Weissert R, Bhaskar SMM. Emerging role of white matter lesions in cerebrovascular disease. *Eur J Neurosci*. 2021;54(4):5531-5559. doi:10.1111/ejn.15379.

4. Shi C, Killingsworth MC, Bhaskar SMM. Prognostic capacity of hyperdense middle cerebral artery sign in anterior circulation acute ischaemic stroke patients receiving reperfusion therapy: A systematic review and meta-analysis. *Acta Neurol Belg*. 2021:1-13. doi:10.1007/s13760-021-01720-3.

5. Katyal A, Calic Z, Killingsworth M, Bhaskar SMM. Diagnostic and prognostic utility of computed tomography perfusion imaging in posterior circulation acute ischemic stroke: A systematic review and meta-analysis. *Eur J Neurol*. 2021;28(8):2657-2668. doi:10.1111/ene.14934.

6. Ravindran AV, Killingsworth MC, Bhaskar S. Cerebral collaterals in acute ischaemia: Implications for acute ischaemic stroke patients receiving reperfusion therapy. *Eur J Neurosci*. 2021;53(4):1238-1261. doi:10.1111/ejn.14955.

7. Chugh C. Acute ischemic stroke: Management approach. *Indian J Crit Care Med*. 2019;23(suppl 2):S140-S146. doi:10.5005/jp-journals-10071-23192.

8. Bhaskar S, Stanwell P, Cordato D, Attia J, Levi C. Reperfusion therapy in acute ischemic stroke: Dawn of a new era?. *BMC Neurol*. 2018;18(1):8. doi:10.1186/s12883-017-1007-y.

9. Khoshnam SE, Winlow W, Farzaneh M, Farbood Y, Moghaddam HF. Pathogenic mechanisms following ischemic stroke. *Neurol Sci*. 2017;38(7):1167-1186. doi:10.1007/s10072-017-2938-1.

10. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708-718. doi:10.1056/NEJMoa1713973.

11. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21. doi:10.1056/NEJMoa1706442.

12. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: A guideline for healthcare professionals from the American heart association/American stroke association. *Stroke*. 2019;50(12):e344-e418. doi:10.1161/STR.0000000000000211.

13. Sweid A, Hammoud B, Ramesh S, et al. Acute ischaemic stroke interventions: Large vessel occlusion and beyond. *Stroke Vasc Neurol*. 2020;5(1):80-85. doi:10.1136/svn-2019-000262.

14. Sharma D, Spring KJ, Bhaskar SMM. Neutrophil-lymphocyte ratio in acute ischemic stroke: Immunopathology, management, and prognosis. *Acta Neurol Scand*. 2021;144(5):486-499. doi:10.1111/ane.13493.

15. Anrather J, Iadecola C. Inflammation and stroke: An overview. *Neurotherapeutics*. 2016;13(4):661-670. doi:10.1007/s13311-016-0483-x.

16. Jian Z, Liu R, Zhu X, et al. The involvement and therapy target of immune cells after ischemic stroke. Review. *Front Immunol*. 2019;10(2167):2167. doi:10.3389/fimmu.2019.02167.

17. Malone K, Amu S, Moore AC, Waeber C. The immune system and stroke: From current targets to future therapy. *Immunol Cell Biol*. 2019;97(1):5-16. doi:10.1111/imcb.12191.

18. Nakamura A, Otani K, Shichita T. Lipid mediators and sterile inflammation in ischemic stroke. *Int Immunol*. 2020;32(11):719-725. doi:10.1093/intimm/dxaa027.

19. Petrovic-Djergovic D, Goonewardena SN, Pinsky DJ. Inflammatory disequilibrium in stroke. *Circ Res*. 2016;119(1):142-158. doi:10.1161/CIRCRESAHA.116.308022.

20. Planas AM. Role of immune cells migrating to the ischemic brain. *Stroke*. 2018;49(9):2261-2267. doi:10.1161/STROKEAHA.118.021474.

21. Berchtold D, Priller J, Meisel C, Meisel A. Interaction of microglia with infiltrating immune cells in the different phases of stroke. *Brain Pathol*. 2020;30(6):1208-1218. doi:10.1111/bpa.12911.

22. Lei TY, Ye YZ, Zhu XQ, et al. The immune response of T cells and therapeutic targets related to regulating the levels of T helper cells after ischaemic stroke. *J Neuroinflammation*. 2021;18(1):25. doi:10.1186/s12974-020-02057-z.

23. Xu S, Lu J, Shao A, Zhang JH, Zhang J. Glial Cells: Role of the Immune Response in Ischemic Stroke. *Front Immunol*. 2020;11:294. doi:10.3389/fimmu.2020.00294.

24. Rayasam A, Hsu M, Kijak JA, et al. Immune responses in stroke: How the immune system contributes to damage and healing after stroke and how this knowledge could be translated to better cures? *Immunology*. 2018;154(3):363-376. doi:10.1111/imm.12918.

25. Lattanzi S, Brigo F, Trinka E, Cagnetti C, Di Napoli M, Silvestrini M. Neutrophil-to-lymphocyte ratio in acute cerebral hemorrhage: A system review. *Transl Stroke Res*. 2019;10(2):137-145. doi:10.1007/s12975-018-0649-4.

26. Sabouri E, Majdi A, Jangjui P, Rahigh Aghsan S, Naseri Alavi SA. Neutrophil-to-lymphocyte ratio and traumatic brain injury: A review study. *World Neurosurg*. 2020;140:142-147. doi:10.1016/j.wneu.2020.04.185.

27. Soulaiman SE, Dopa D, Raad AT, et al. Cohort retrospective study: The neutrophil to lymphocyte ratio as an independent predictor of outcomes at the presentation of the multi-trauma patient. *Int J Emerg Med*. 2020;13(1):5. doi:10.1186/s12245-020-0266-3.

28. Tanriverdi Z, Gungoren F, Tascanov MB, Besli F, Altiparmak IH. Comparing the diagnostic value of the C-reactive protein to albumin ratio with other inflammatory markers in patients with stable angina pectoris. *Angiology*. 2020;71(4):360-365. doi:10.1177/0003319719897490.

29. Tanriverdi Z, Colluoglu T, Dursun H, Kaya D. The relationship between neutrophil-to-lymphocyte ratio and fragmented QRS in acute STEMI patients treated with primary PCI. *J Electrocardiol*. 2017;50(6):876-883. doi:10.1016/j.jelectrocard.2017.06.011.

30. Chen C, Cong BL, Wang M, et al. Neutrophil to lymphocyte ratio as a predictor of myocardial damage and cardiac dysfunction in acute coronary syndrome patients. *Interg Med Res*. 2018;7(2):192-199. doi:10.1016/j.imr.2018.02.006.

31. Zhang S, Diao J, Qi C, et al. Predictive value of neutrophil to lymphocyte ratio in patients with acute ST segment elevation myocardial infarction after percutaneous coronary intervention: A meta-analysis. *BMC Cardiovasc Disord*. 2018;18(1):75. doi:10.1186/s12872-018-0812-6.

32. Maestrini I, Strbian D, Gautier S, et al. Higher neutrophil counts before thrombolysis for cerebral ischemia predict worse outcomes. *Neurology*. 2015;85(16):1408-1416. doi:10.1212/WNL.0000000000002029.

33. Malhotra K, Goyal N, Chang JJ, et al. Differential leukocyte counts on admission predict outcomes in patients with acute ischaemic stroke treated with intravenous thrombolysis. *Eur J Neurol*. 2018;25(12):1417-1424. doi:10.1111/ene.13741.

34. Song SY, Zhao XX, Rajah G, et al. Clinical significance of baseline neutrophil-to-lymphocyte ratio in patients with ischemic stroke or hemorrhagic stroke: An updated meta-analysis. *Front Neurol*. 2019;10:1032. doi:10.3389/fneur.2019.01032.

35. Duan Z, Wang H, Wang Z, et al. Neutrophil-lymphocyte ratio predicts functional and safety outcomes after endovascular treatment for acute ischemic stroke. *Cerebrovasc Dis*. 2018;45(5-6):221-227. doi:10.1159/000489401.

36. Sengeze N, Giray S. The relationship between first pass recanalization of stent-retriever-based thrombectomy and neutrophil to lymphocyte ratio in middle cerebral artery occlusions. *Int J Neurosci*. 2021;131(7):634-640. doi:10.1080/00207454.2020.1838513.

37. Wang L, Song Q, Wang C, et al. Neutrophil to lymphocyte ratio predicts poor outcomes after acute ischemic stroke: A cohort study and systematic review. *J Neurol Sci*. 2019;406:116445. doi:10.1016/j.jns.2019.116445.

38. Zhang J, Ren Q, Song Y, et al. Prognostic role of neutrophil-lymphocyte ratio in patients with acute ischemic stroke. *Medicine (Baltim)*. 2017;96(45):e8624. doi:10.1097/MD.0000000000008624.

39. Goyal N, Tsivgoulis G, Chang JJ, et al. Admission neutrophil-to-lymphocyte ratio as a prognostic biomarker of outcomes in large vessel occlusion strokes. *Stroke*. 2018;49(8):1985-1987. doi:10.1161/STROKEAHA.118.021477.

40. Zhang R, Wu X, Hu W, et al. Neutrophil-to-lymphocyte ratio predicts hemorrhagic transformation in ischemic stroke: A meta-analysis. *Brain Behav*. 2019;9(9):e01382. doi:10.1002/brb3.1382.

41. Paudel SS, Thapa B, Luitel R. Neutrophil lymphocyte ratio as a prognostic marker in acute ischemic stroke: A systematic review and meta-analysis. *J Nepal Health Res Counc*. 2021;18(4):573-579. doi:10.33314/jnhrc.v18i4.3143.

42. Wan J, Wang X, Zhen Y, et al. The predictive role of the neutrophil-lymphocyte ratio in the prognosis of adult patients with stroke. *Chin Neurosurg J*. 2020;6:22. doi:10.1186/s41016-020-00201-5.

43. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ*. 2009;339:b2700. doi:10.1136/bmj.b2700.

44. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: An updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527. doi:10.1136/bmj.h5527.

45. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA*. 2000;283(15):2008-2012. doi:10.1001/jama.283.15.2008.

46. Bhaskar S, Stanwell P, Bivard A, et al. The influence of initial stroke severity on mortality, overall functional outcome and in-hospital placement at 90 days following acute ischemic stroke: A tertiary hospital stroke register study. *Neurol India*. 2017;65(6):1252-1259. doi:10.4103/0028-3886.217947.

47. Shen YW, Zhang XM, Lv M, et al. Utility of gonadotropin-releasing hormone agonists for prevention of chemotherapy-induced ovarian damage in premenopausal women with breast cancer: A systematic review and meta-analysis. *OncoTargets Ther*. 2015;8:3349-3359. doi:10.2147/OTT.S95936.

48. Chowdhury SZ, Baskar PS, Bhaskar S. Effect of prehospital workflow optimization on treatment delays and clinical outcomes in acute ischemic stroke: A systematic review and meta-analysis. *Acad Emerg Med*. 2021;28(7):781-801. doi:10.1111/acem.14204.

49. Saunders R, Struys M, Pollock RF, Mestek M, Lightdale JR. Patient safety during procedural sedation using capnography monitoring: A systematic review and meta-analysis. *BMJ Open*. 2017;7(6):e013402. doi:10.1136/bmjopen-2016-013402.

50. Deeks JJHJ, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPTTJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds *Cochrane Handbook for Systematic Reviews of Interventions version 62*. Cochrane; 2021.

51. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat Methods Med Res*. 2018;27(6):1785-1805. doi:10.1177/0962280216669183.

52. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14(1):135. doi:10.1186/1471-2288-14-135.

53. Walter SD, Yao X. Effect sizes can be calculated for studies reporting ranges for outcome variables in systematic reviews. *J Clin Epidemiol*. 2007;60(8):849-852. doi:10.1016/j.jclinepi.2006.11.003.

54. Topcuoglu MA, Pektezel MY, Yilmaz E, Arsava EM. Systemic inflammation indices in patients with acute ischemic stroke treated with intravenous tissue plasminogen activator: Clinical yield and utility. *Angiology*. 2021;72(3):279-284. doi:10.1177/0003319720969997.

55. Lux D, Alakbarzade V, Bridge L, et al. The association of neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio with 3-month clinical outcome after mechanical thrombectomy following stroke. *J Neuroinflammation*. 2020;17(1):60. doi:10.1186/s12974-020-01739-y.

56. Aly M, Abdalla RN, Batra A, et al. Follow-up neutrophil-lymphocyte ratio after stroke thrombectomy is an independent biomarker of clinical outcome. *J Neurointerv Surg*. 2021;13(7):609-613. doi:10.1136/neurintsurg-2020-016342.

57. Sarioglu O, Capar AE, Bas Sokmez DF, Topkaya P, Belet U. Relationship between the first pass effect and the platelet-lymphocyte ratio in acute ischemic stroke. *Interv Neuroradiol*. 2021;27(4):523-530. doi:10.1177/1591019920976251.

58. Switonska M, Piekus-Slomka N, Slomka A, Sokal P, Zekanowska E, Lattanzi S. Neutrophil-to-lymphocyte ratio and symptomatic hemorrhagic transformation in ischemic stroke patients undergoing revascularization. *Brain Sci*. 2020;10(11):1-9. doi:10.3390/brainsci10110771.

59. Chen Z, He Y, Su Y, Sun Y, Zhang Y, Chen H. Association of inflammatory and platelet volume markers with clinical outcome in patients with anterior circulation ischaemic stroke after endovascular thrombectomy. *Neurol Res*. 2021;43(6):503-510. doi:10.1080/01616412.2020.1870359.

60. Inanc Y, Inanc Y. The effects of neutrophil to lymphocyte and platelet to lymphocyte ratios on prognosis in patients undergoing mechanical thrombectomy for acute ischemic stroke. *Ann Ital Chir*. 2018;89:367-373.

61. Gong P, Liu Y, Gong Y, et al. The association of neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio with post-

thrombolysis early neurological outcomes in patients with acute ischemic stroke. *J Neuroinflammation*. 2021;18(1):51. doi:10.1186/s12974-021-02090-6.

62. Ferro D, Matias M, Neto J, et al. Neutrophil-to-lymphocyte ratio predicts cerebral edema and clinical worsening early after reperfusion therapy in stroke. *Stroke*. 2021; 52(3):859-867. doi:10.1161/STROKEAHA.120.032130.

63. Balta S, Celik T, Mikhailidis DP, et al. The relation between atherosclerosis and the neutrophil-lymphocyte ratio. *Clin Appl Thromb Hemost*. 2016;22(5):405-411. doi: 10.1177/1076029615569568.

64. Ying A, Cheng Y, Lin Y, Yu J, Wu X, Lin Y. Dynamic increase in neutrophil levels predicts parenchymal hemorrhage and function outcome of ischemic stroke with r-tPA thrombolysis. *Neurol Sci*. 2020;41(8):2215-2223. doi:10.1007/s10072-020-04324-6.

65. Sandor-Keri J, Benedek I, Polexa S, Benedek I. The link between SARS-CoV-2 infection, inflammation and hypercoagulability-impact of hemorheologic alterations on cardiovascular mortality. *J Clin Med*. 2021(14):10. doi:10.3390/jcm10143015.

66. Bhaskar S, Sharma D, Walker AH, et al. Acute neurological care in the COVID-19 era: The pandemic health system resilience PROGRAM (REPROGRAM) consortium pathway. *Front Neurol*. 2020;11:579. doi:10.3389/fneur.2020.0057910.3389/fneur.2020.00579.

67. Tang R, Yang H, Choi JR, et al. Capillary blood for point-of-care testing. *Crit Rev Clin Lab Sci*. 2017;54(5):294-308. doi:10.1080/10408363.2017.1343796.

68. Sharma D, Bhaskar S. Addressing the Covid-19 burden on medical education and training: The role of telemedicine and tele-education during and beyond the pandemic. *Front Public Health*. 2020;8:589669. doi:10.3389/fpubh.2020.589669.

69. Kocaturk O, Besli F, Gungoren F, Kocaturk M, Tanriverdi Z. The relationship among neutrophil to lymphocyte ratio, stroke territory, and 3-month mortality in patients with acute ischemic stroke. *Neurol Sci*. 2019;40(1):139-146. doi:10.1007/s10072-018-3604-y.

70. Charbonnier G, Bonnet L, Biondi A, Moulin T. Intracranial bleeding after reperfusion therapy in acute ischemic stroke. *Rev Front Neurol*. 2021;11(1958): 629920. doi:10.3389/fneur.2020.629920.

71. Semerano A, Laredo C, Zhao Y, et al. Leukocytes, collateral circulation, and reperfusion in ischemic stroke patients treated with mechanical thrombectomy. *Stroke*. 2019;50(12):3456-3464. doi:10.1161/STROKEAHA.119.026743.

72. Komurcu HF, Gozke E, Dogan AP, Kalyoncu Aslan I, Salt I, Ozgenc Bi Er CI. Changes in neutrophil, lymphocyte, platelet ratios and their relationship with NIHSS after rtPA and/or thrombectomy in ischemic stroke. *J Stroke Cerebrovasc Dis*. 2020;29(8):105004. doi:10.1016/j.jstrokecerebrovasdis.2020.105004.

73. Shi J, Peng H, You S, et al. Increase in neutrophils after recombinant tissue plasminogen activator thrombolysis predicts poor functional outcome of ischaemic stroke: A longitudinal study. *Eur J Neurol*. 2018;25(4):687-e45. doi:10.1111/ene.13575.

74. Brooks SD, Spears C, Cummings C, et al. Admission neutrophil-lymphocyte ratio predicts 90 day outcome after endovascular stroke therapy. *J Neurointerv Surg*. 2014; 6(8):578-583. doi:10.1136/neurintsurg-2013-010780.

75. Li F, Ren Y, Cui X, et al. Postoperative hyperglycemia predicts symptomatic intracranial hemorrhage after endovascular treatment in patients with acute anterior circulation large artery occlusion. *J Neurol Sci*. 2020;409:116588. doi:10.1016/j.jns.2019.116588.

76. Liu YL, Lu JK, Yin HP, et al. High neutrophil-to-lymphocyte ratio predicts hemorrhagic transformation in acute ischemic stroke patients treated with intravenous thrombolysis. *Int J Hypertens*. 2020;2020:5980261. doi:10.1155/2020/5980261.

77. Meng L, Wang H, Yang H, et al. Nomogram to predict poor outcome after mechanical thrombectomy at older age and histological analysis of thrombus composition. *Oxid Med Cell Longev*. 2020;2020:8823283. doi:10.1155/2020/8823283.

78. Pagram H, Bivard A, Lincz LF, Levi C. Peripheral immune cell counts and advanced imaging as biomarkers of stroke outcome. *Cerebrovasc Dis Extra*. 2016;6(3): 120-128. doi:10.1159/000450620.

79. Pikija S, Sztriha LK, Killer-Oberpfalzer M, et al. Neutrophil to lymphocyte ratio predicts intracranial hemorrhage after endovascular thrombectomy in acute ischemic stroke. *J Neuroinflammation*. 2018;15(1):319. doi:10.1186/s12974-018-1359-2.

80. Tian C, Ji Z, Xiang W, et al. Association of lower leukocyte count before thrombolysis with early neurological improvement in acute ischemic stroke patients. *J Clin Neurosci*. 2018;56:44-49. doi:10.1016/j.jocn.2018.08.004.

81. Chen Y, Ren J, Yang N, et al. Eosinophil-to-monocyte ratio is a potential predictor of prognosis in acute ischemic stroke patients after intravenous thrombolysis. *Clin Interv Aging*. 2021;16:853-862.

82. Cheng Y, Ying A, Lin Y, et al. Neutrophil-to-lymphocyte ratio, hyperglycemia, and outcomes in ischemic stroke patients treated with intravenous thrombolysis. *Brain Behav*. 2020;10(9):e01741. doi:10.1002/brb3.1741.

83. Guo Z, Yu S, Xiao L, et al. Dynamic change of neutrophil to lymphocyte ratio and hemorrhagic transformation after thrombolysis in stroke. *J Neuroinflammation*. 2016;13(1):199. doi:10.1186/s12974-016-0680-x.

84. Hu D, Ding C, Jiang X, et al. Elevated levels of inflammation markers predict poor outcomes in acute ischemic stroke patients after intravenous thrombolysis. *J Stroke Cerebrovasc Dis*. 2021;30(3):105587. doi:10.1016/j.jstrokecerebrovasdis.2020.105587.

85. Li X, Wu F, Jiang C, et al. Novel peripheral blood cell ratios: Effective 3-month post-mechanical thrombectomy prognostic biomarkers for acute ischemic stroke patients. *J Clin Neurosci*. 2021;89:56-64. doi:10.1016/j.jocn.2021.04.013.

86. Liu YL, Wu ZQ, Qu JF, et al. High neutrophil-to-lymphocyte ratio is a predictor of poor short-term outcome in patients with mild acute ischemic stroke receiving intravenous thrombolysis. *Brain Behav*. 2020;10(12):e01857. doi:10.1002/brb3.1857.

87. Lv S, Song Y, Zhang F-L, et al. Early prediction of the 3-month outcome for individual acute ischemic stroke patients who received intravenous thrombolysis using the N2H3 nomogram model. *Ther Adv Neurol Disord*. 2020;13: 1756286420953054. doi:10.1177/1756286420953054.

88. Oh SW, Yi HJ, Lee DH, Sung JH. Prognostic significance of various inflammation-based scores in patients with mechanical thrombectomy for acute ischemic stroke. *World Neurosurg*. 2020;141:e710-e717. doi:10.1016/j.wneu.2020.05.272.

89. Oren O, Haki C, Kaya H, Yuksel M. Predictive value of admission neutrophil/lymphocyte ratio in symptomatic intracranial hemorrhage after stroke thrombolysis. *Neurol Sci*. 2022;43:435-440. doi:10.1007/s10072-021-05326-8.

90. Ozgen E, Guzel M, Akpinar CK, Yucel M, Demir MT, Baydin A. The relationship between neutrophil/lymphocyte, monocyte//lymphocyte, platelet/lymphocyte ratios and clinical outcomes after ninety days in patients who were diagnosed as having acute ischemic stroke in the emergency room and underwent a mechanical thro. *Bratisl Lek Listy*. 2020;121(9):634-639. doi:10.4149/BLL_2020_102.

91. Shi Z, Guo S, Pan J, Xu C, Geng Y, Zheng S. Increased postoperative fasting glucose is associated with unfavorable outcomes in patients treated with mechanical thrombectomy treatment. *Front Neurol*. 2021;12:668363.

92. Zhu Y, Gao J, Lv Q, Yin Q, Yang D. Risk factors and outcomes of stroke-associated pneumonia in patients with stroke and acute large artery occlusion treated with endovascular thrombectomy. *J Stroke Cerebrovasc Dis*. 2020;29(11):105223. doi:10.1016/j.jstrokecerebrovasdis.2020.105223.

93. Feng X, Ye G, Cao R, et al. Identification of predictors for hemorrhagic transformation in patients with acute ischemic stroke after endovascular therapy using the decision tree model. *Clin Interv Aging*. 2020;15:1611-1624. doi:10.2147/CIA.S257931.

94. Deng QW, Gong PY, Chen XL, et al. Admission blood cell counts are predictive of stroke-associated infection in acute ischemic stroke patients treated with endovascular therapy. *Neurol Sci*. 2021;42(6):2397-2409. doi:10.1007/s10072-020-04827-2.