Neutrophil-to-Lymphocyte Ratio and Response to Intravenous Thrombolysis in Patients with Acute Ischemic Stroke

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Background and Aims: The Neutrophil-to-Lymphocyte Ratio (NLR) is suggested as a readily available and inexpensive biomarker to predict prognosis of acute stroke. Experience with intravenous (IV) tissue plasminogen activator (tPA) treatment is limited. *Methods:* Total 142 (80 female, age: 69 ± 13 yearr) consecutive acute stroke patients treated with IV tPA were evaluated. Admission and 24th hour lymphocyte, neutrophil, and monocyte counts were measured and the NLR was calculated. *Results:* Average NLR elevated (by 3.47 ± 6.75) significantly from admission to 24th hour ($P < .001$). Total 52% of patients exerted good response to IV tPA (NIHSS ≤1 or decrease in NIHSS ≥4 at end of 24 hour), while 27% showed dramatic response (decrease in NIHSS ≥8 at end of 24 hour). The patients with "thrombolysis resistance" had significantly higher 24 hour Neutrophil-to-Lymphocyte Ratio (24h NLR) ($P = .001$). At the end of 3rd month, 46.5% of patients had favorable (modified Rankin's score, mRS 0-2) and 32.4% had excellent (mRS 0-1) outcome. Patients without favorable/excellent outcome had significantly higher 24h NLRs. Regression analysis indicated that post-tPA, but not admission NLR, was an independent negative predictor of excellent ($\beta = -.216$, $P = .006$) and favorable ($\beta = -.179$, $P = .034$) outcome after adjustment for age, hypertension, and admission NIHSS. Nine patients who developed symptomatic intracerebral hemorrhage had elevated pre-tPA (7.6 ± 7.39 versus 3.33 ± 3.07, $P < .001$) and 24h NLR (26.2 ± 18.6 versus 5.78 ± 4.47, $P < .001$). Of note, receiver operating characteristics analysis failed to detect any reliable NLR threshold for absence of tPA effectiveness/dramatic response, 3rd month good/excellent outcome or any type tPA-induced hemorrhage. *Conclusions:* As a marker of stroke-associated acute stress response, the NLR, which increases during the first 24 hours, is an epiphenomenon of poor prognosis. However, pretreatment NLR values have no importance in predicting IV tPA response.

Key Words: Acute stroke—tissue plasminogen activator—disability—inflammation—lymphocyte—immunodepression

Introduction

The Neutrophil-to-Lymphocyte Ratio (NLR) is suggested as a readily available and inexpensive biomarker to predict prognosis of patients with acute stroke in the emergency phase.[1] Experience reaching almost up to 5000 patients indicates that higher admission NLR is associated with higher odds of mortality, poor functional outcome at discharge and 3 months, increase in length of hospital stay, and expenses in patients with not only ischemic stroke,[2–4] but also acute intracerebral hemorrhage.[5,6]

Experience regarding the prognostic role of NLR among acute stroke patients treated with systemic thrombolysis using intravenous (IV) recombinant tissue plasminogen activator (tPA)[7–9] and/or endovascular thrombectomy is

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The complete de-identified dataset is available from the corresponding author on a reasonable request.

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limited.[10–12] In addition, it is not easy to employ the results of IV tPA studies focusing on this subject into the clinical arena due to the inclusion of relatively modest cases in these cohorts such as those with low National Institute of Health Stroke Scale (NIHSS) score or small infarcts, as severe cases are nowadays directed to thrombectomy[8]; or due to the use of heterogeneous cohorts which also include patients undergoing bridging treatment (IV tPA then thrombectomy).[7,9] This perspective led us to study the subject in a standard and homogeneous population of patients who only received IV tPA, in an effort to better reflect the interplay between complete blood count (CBC) profile and thrombolysis response. In addition to determine the position of NLR in predicting post-tPA hemorrhage risk and prognosis at the third month, its modifying effect on acute response to IV tPA was herein focused for the first time.

Methods

Patients

A total of 142 (80 female, mean ± standard deviation of age: 69 ± 13 years) consecutive acute stroke patients treated with IV tPA, over the last 9 years, were evaluated as part of this retrospective analysis. Clinical and imaging data were extracted from our prospectively gathered institutional stroke database, that utilizes a protocolized stepwise etiological work-up including transthoracic echocardiography, 24-hour Holter monitoring, cranial magnetic resonance imaging along with at least 1 craniocervical angiography modality. In all patients, standard IV tPA application protocols and metrics were largely followed. The institutional ethics board approved the study protocol and the database. Patients treated with interventional techniques such as thrombectomy were excluded.

Clinical stroke severity was assessed with NIHSS at admission, at 24 hours after IV tPA and at discharge.[13] Functional outcome was evaluated with modified Rankin's score (mRS) at the end of the third month.[14] "Effective response" to IV tPA was defined as a decrease of NIHSS ≥ 4, or drop to 0 or 1 at the end of 24 hours after IV tPA. "Dramatically good response" to IV tPA was defined when NIHSS decrease was equal to or greater than 8.[15] "Favorable" outcome was defined when mRS was 3 or less; while "excellent" outcome was diagnosed when mRS was 0 or 1. Stroke etiological classification was performed by using the Causative Classification of Stroke algorithm.[16]

Hematological Data

CBC data were collected via electronic chart review. Twelve patients treated with IV tPA during the same period but without 24th hour CBC values were excluded. Studied parameters and their normal ranges were lymphocyte count, 1.2-3.6 ($10^3/\mu L$); neutrophil count, 1.8-6.4 ($10^3/\mu L$); monocyte count, .3-.9 ($10^3/\mu L$); hemoglobin, 11.7-15.5 (g/dL), and hematocrit 34.5-46.3 (%). Normal limits of NLR were calculated as .5-5.3.

Statistics

All values are represented as mean ± standard deviation SD, 95% confidence intervals [95% CI], percentages, medians with interquartile ranges as appropriate. Distribution normality was analyzed with the Kolmogorov-Smirnov and Shapiro-Wilk tests properly. Differences were tested with Mann-Whitney *U*/Student's *t*, paired *t* and Chi-square/exact tests appropriately. Exploratory multivariate models to detect importance of NLR and other CBC parameters in response to tPA, tPA-associated symptomatic intraparenchymal hemorrhage, effectiveness of IV tPA, and 3-month favorable outcome were constructed. In these models, factors with *P*value less than 0.1 in the univariate phase were included into the multivariate steps. The area under the curve[17] of receiver operating characteristics[8] (ROC) curve was produced to determine accuracy and threshold of NLR values for tPA ineffectiveness, hemorrhage, and poor prognosis rates. Accuracy was considered "excellent" for .90-1.0 of lower limit of 95% CI of area under curve (AUC) of ROC curve, "good" for .80-.89, "fair" for .70-.79, "poor" for .60-.69, and "failed" for less than .60. $P < .05$ was set as the statistical significance level. SPSS version 22 was used for all calculations.

Results

Average lymphocyte count decreased significantly from admission to 24th hour (by .65 ± .88 from 2.14 ± 1.15 to 1.49 ± .8, $10^3/\mu L$, $P < .001$). Lymphopenia (<1.2, $10^3/\mu L$) was diagnosed in 13% of patients at admission and in 32% at 24th hour. Lymphocytosis (>3.6, $10^3/\mu L$) was seen in 8% at admission and none at 24th hour. During the first 24 hours, lymphocyte count decreased numerically in 78.2%, increased in 16.2%, and stayed in the same range in 5.6%. Average neutrophil count increased significantly from admission to 24th hour (by 1.65 ± 2.85 from 5.76 ± 2.6 to 7.41 ± 4.05, $10^3/\mu L$, $P < .001$). Frequency of neutrophilia (>6.4, $10^3/\mu L$) doubled from admission to 24th hour (25.7%-51%). Absolute neutrophil count increased in 63.4%, decreased in 31.4%, and remained in the same level in 5.2% of the patients within the first day. Reflecting these changes, NLR significantly elevated by 3.47 ± 6.75 from admission to the end of the first day (from 3.58 ± 2.4 to 7.04 ± 5.1, $P < .001$). Total leukocyte and monocyte count, hemoglobin and hematocrit values did not change significantly during the first day. Of note, 24th hour NLR was found to be highly correlated with stroke severity as measured by NIHSS ($r = .496$, $P < .001$), while no positive correlation was present with admission NLR ($r = .023$, $P = .779$). None of the patients had fever or other signs of infection, apparent elevation of CRP (measured in 48%), or significantly high erythrocyte

sedimentation rate (in 54%). And also, no history of usage of medicine with potential impact on NLR such as steroids, was elicited.

Response to IV tPA was effective in 52% and excellent in 27%. Absence of good response to IV tPA connected to higher post-tPA hemorrhage rates and extended length of stay. Excellent response was more frequent in patients without angiographically-documented arterial occlusion. Due to significantly lower neutrophil and nonsignificantly higher lymphocyte counts, admission NLR was marginally lower in patients with good response to IV tPA (*P*values were .071 for effective response and .047 for dramatic response). The connection of the lytic response and the CBC parameters became more pronounced at the end of the first day albeit with presence of considerable variation. At 24th hour, patients with poor IV tPA response, so-called "thrombolytic resistance," had significantly higher NLR values (*P*values were .001 for effective response and .004 for dramatic response), driven by both significant neutrophil increase and lymphocyte decrease (Table 1). AUC of ROC curve of NLR was failed to detect a reliable threshold for tPA ineffectiveness and absence of dramatic response for the pre-tPA bolus time epoch. In contrast, 24-hour NLR higher than 3.2 indicates, albeit with poor quality yet still significant, a decrease of tPA effectiveness (sensitivity 48%, specificity 84%) and values higher than 6.3 indicate a decrease of dramatic response to tPA (sensitivity 89.5%, specificity 45%) (Table 4A).

In patients receiving IV tPA, excellent (mRS 0-1) outcome was noted in 32.4% and favorable outcome in 46.5%. While no difference of admission CBC indices were noted, patients without favorable and excellent outcome had lower lymphocyte, higher neutrophil and white blood cell, and correspondingly highly significantly elevated NLRs compared to those with worse prognosis (Table 2). An exploratory regression model indicated that post-tPA NLR was independent negative predictor ($\beta = -.216$, $P = .006$) of excellent outcome after adjustment for age ($\beta = -.082$, $P = .319$), presence of hypertension ($\beta = -.260$, $P = .001$), and admission NIHSS ($\beta = -.220$, $P = .005$). A similar model repeated for favorable outcome indicated that post-treatment NLR was again a significant

Table 1. *Response to IV tPA*

	Effective response			Excellent response		
	Yes (n = 73)	No (n = 69)	*P*	Yes (n = 38)	No (n = 104)	*P*
Age	69 ± 13	69 ± 13	0.914	70 ± 14	69 ± 12	0.606
Female gender	56%	54%	0.761	61%	53%	0.418
BMI	29 ± 6	28 ± 5	0.930	29 ± 8	27 ± 5	0.232
Hypertension	63%	74%	0.163	55%	73%	0.043
Diabetes	27%	21%	0.321	19%	26%	0.351
Atrial fibrillation	29%	39%	0.192	29%	36%	0.460
Time to door (min)	77 ± 37	80 ± 45	0.692	90 ± 47	74 ± 38	0.042
NIHSS admission	13.5 ± 5	14.4 ± 6	0.354	13.2 ± 6	14.2 ± 6	0.331
Time to needle (min)	151 ± 48	168 ± 58	0.048	165 ± 59	157 ± 52	0.430
Length of stay	17 ± 25	26 ± 27	0.029	13 ± 19	25 ± 28	0.023
Any bleeding	21%	36%	0.038	13%	34%	0.016
PH2 bleeding	1.4%	11.6%	0.012	0%	9%	0.055
M1/TICA/BA occlusion	45%	52%	0.406	45%	50%	0.579
No occlusion	19%	12%	0.212	29%	11%	0.007
Hematological indices						
Admission Lymphocyte	2.26 ± 1.06	2.03 ± 1.02	0.198	2.28 ± 1.09	2.1 ± 1.03	0.367
Admission Neutrophil	5.22 ± 2.15	6.36 ± 3.41	0.017	4.97 ± 1.52	6.06 ± 3.2	0.045
Admission NLR	3.05 ± 2.83	4.15 ± 4.23	0.071	2.59 ± 1.36	3.95 ± 4.08	0.047
Admission WBC	8.28 ± 2.23	9.42 ± 3.43	0.020	8.19 ± 2.08	9.07 ± 3.15	0.111
Admission Hematocrit	39.8 ± 4.26	40.69 ± 5.23	0.269	40.02 ± 4.46	40.31 ± 4.88	0.750
Admission Hemoglobin	13.3 ± 1.46	13.62 ± 1.95	0.275	13.36 ± 1.6	13.49 ± 1.76	0.690
Admission Monocyte	0.66 ± 0.26	0.65 ± 0.28	0.762	0.67 ± 0.22	0.65 ± 0.28	0.830
Post-tPA Lymphocyte	1.66 ± 0.77	1.32 ± 0.57	0.064	1.74 ± 0.78	1.41 ± 0.65	0.013
Post-tPA Neutrophil	6.19 ± 2.38	8.77 ± 4.05	<0.001	5.66 ± 1.74	8.1 ± 3.79	<0.001
Post-tPA NLR	4.9 ± 4.01	9.41 ± 10.17	0.001	3.94 ± 2.08	8.25 ± 8.94	0.004
Post-tPA WBC	8.82 ± 2.68	11.05 ± 4.17	<0.001	8.35 ± 2.05	10.47 ± 3.94	0.002
Post-tPA Hematocrit	38.79 ± 4.42	39.16 ± 4.98	0.638	39.08 ± 4.65	38.93 ± 4.72	0.872
Post-tPA Hemoglobin	12.81 ± 2.11	13.04 ± 1.78	0.483	12.72 ± 2.61	13 ± 1.66	0.441
Post-tPA Monocyte	0.63 ± 0.27	0.64 ± 0.29	0.689	0.63 ± 0.25	0.64 ± 0.29	0.926

Abbreviations: BA, Basilar artery; BMI, Body mass index; ICA, internal carotid artery; IV, Intravenous; M1, the first segment of the middle cerebral artery (MCA); min, minute;NIHSS, National Institute of Health Stroke Scale; NLR, Neutrophil-to-Lymphocyte ratio; PH2, Parenchymal Hemorrhage type 2; tPA, recombinant tissue plasminogen activator; WBC, White blood cell.

Table 2. *Long-term prognosis*

	Excellent outcome [mRS ≤ 1]			Favorable outcome [mRS ≤ 2]		
	Yes (n = 46)	No (n = 96)	*P*	Yes (n = 66)	No (n = 76)	*P*
Age	65 ± 13	71 ± 12	0.005	66 ± 14	72 ± 12	0.003
Female gender	59%	53%	0.532	52%	58%	0.446
BMI	27 ± 6	28 ± 6	0.555	29 ± 7	27 ± 4	0.063
Hypertension	48%	78%	<0.001	58%	78%	0.012
Diabetes	20%	26%	0.397	23%	25%	0.752
Atrial fibrillation	30%	35%	0.557	27%	40%	0.125
Time to door (min)	82 ± 40	77 ± 41	0.465	83 ± 46	75 ± 36	0.233
NIHSS admission	11.5 ± 5.5	15.1 ± 5.4	<0.001	11.2 ± 5.2	16.3 ± 5.0	<0.001
Time to needle (min)	159 ± 54	159 ± 54	0.986	161 ± 56	157 ± 51	0.685
Length of stay	11 ± 6	26 ± 31	0.001	11 ± 6	30 ± 34	<0.001
Any bleeding	17%	33%	0.048	20%	36%	0.041
PH2 bleeding	0%	9%	0.032	0%	9%	0.004
No occlusion	22%	13%	0.154	18%	13%	0.409
M1/ICA/BA occlusion	41%	52%	0.229	39%	57%	0.041
Hematological indices						
Admission lymphocyte	2.38 ± 1.09	2.04 ± 1	0.071	2.26 ± 1	2.05 ± 1.08	0.229
Admission neutrophil	5.35 ± 1.78	5.98 ± 3.27	0.228	5.66 ± 2.68	5.91 ± 3.06	0.606
Admission NLR	2.89 ± 2.52	3.92 ± 4	0.112	3.36 ± 3.65	3.81 ± 3.61	0.467
Admission WBC	8.72 ± 2.2	8.89 ± 3.22	0.736	8.88 ± 2.77	8.83 ± 3.07	0.916
Admission hematocrit	40.02 ± 5.09	40.33 ± 4.62	0.716	40.42 ± 4.7	40.05 ± 4.87	0.653
Admission hemoglobin	13.36 ± 1.79	13.5 ± 1.69	0.665	13.54 ± 1.67	13.38 ± 1.78	0.569
Admission monocyte	0.65 ± 0.23	0.66 ± 0.28	0.864	0.66 ± 0.21	0.66 ± 0.31	0.956
Post-tPA lymphocyte	1.89 ± 0.81	1.31 ± 0.55	<0.001	1.75 ± 0.75	1.28 ± 0.58	<0.001
Post-tPA neutrophil	5.89 ± 2	8.19 ± 3.86	<0.001	6.19 ± 2.62	8.56 ± 3.85	<0.001
Post-tPA NLR	3.84 ± 2.3	8.65 ± 9.15	0.001	4.36 ± 3.19	9.49 ± 9.88	<0.001
Post-tPA WBC	8.88 ± 2.59	10.39 ± 3.98	0.020	9.02 ± 3.03	10.69 ± 3.96	0.006
Post-tPA hematocrit	39.38 ± 5.42	38.78 ± 4.31	0.473	39.41 ± 5.05	38.6 ± 4.38	0.310
Post-tPA hemoglobin	12.9 ± 2.66	12.94 ± 1.53	0.920	13.01 ± 2.36	12.86 ± 1.55	0.659
Post-tPA monocyte	0.61 ± 0.24	0.65 ± 0.3	0.515	0.62 ± 0.25	0.65 ± 0.31	0.566

Abbreviations: BA, Basilar artery; BMI, Body mass index; ICA, internal carotid artery; IV, Intravenous; M1, the first segment of the middle cerebral artery (MCA); min, minute; NIHSS, National Institute of Health Stroke Scale; NLR, Neutrophil-to-Lymphocyte ratio; PH2, Parenchymal Hemorrhage type 2; tPA, recombinant tissue plasminogen activator; WBC, White blood cell.

independent negative predictor (β = −.179, *P*= .034) after adjustment for age (β = −.039, *P*= .671), documented parent artery occlusion (β = −.098, *P*= .262), presence of hypertension (β = −.192, *P*= .02), and NIHSS (β = −.368, *P*< .001). No significant threshold of admission NLR was found to predict 3-month prognosis (Table 4A). Our ROC analysis indicated a 24 hour NLR higher than 3.6 was an optimal threshold to predict good prognosis, either mRS less than 1 or 2, but lower limit of 95% CI of AUC of ROC was .656 and .647, respectively; representing a poor predictive power (Table 4B).

Admission NLR was found to be significantly higher (4.74 ± 5.29 versus 3.15 ± 2.58, *P*= .018) in patients who developed hemorrhage after tPA. NLR increase was apparently due to neutrophil count increase (Table 3). Nine patients developing PH2 had very significantly elevated pre-tPA NLR (7.6 ± 7.39 versus 3.33 ± 3.07, *P*< .001) definitely due to not only increase of neutrophil count but also decrease of lymphocyte count. The average NLR was elevated significantly in both any hemorrhage (11.64 ± 12.44 versus 5.3 ± 4.14, *P*< .001) and more markedly in PH type 2 (26.2 ± 18.6 versus 5.78 ± 4.47, *P*< .001) (Table 3). In terms of any type tPA-induced hemorrhage, ROC analysis did not document reliable NLR thresholds for neither at admission (lower limit of 95% CI was .525) nor at 24 hours (lower limit of 95% CI was .640). We found that 24th hour NLR higher than 7.4 is a good marker of symptomatic hemorrhage development while admission value was a fair predictor (Table 4A and B).

Discussion

We found that lymphocyte and neutrophil count, and NLR, measured before tPA bolus are not reliable predictors of prognosis and tPA responsiveness in acute stroke patients undergoing systemic thrombolysis. However, high post-treatment 24-hour NLR, which represent "the lymphopenia neutrophilia response," indicates resistance to lytics, poor prognosis, and high hemorrhagic adverse events with

Table 3. *Post-tPA hemorrhage*

	Any hemorrhage			PH type 2		
	Yes (n = 40)	No (n = 102)	p	Yes (n = 9)	No (n = 133)	*P*
Age	70 ± 12	69 ± 13	0.868	67 ± 14	69 ± 13	0.621
Female/male	65%	52%	0.144	56%	55%	0.995
BMI	27 ±5	28 ± 6	0.444	25 ± 5	28 ± 6	0.327
Hypertension	70%	68%	0.814	56%	69%	0.387
Diabetes	28%	22%	0.514	22%	24%	0.910
Atrial fibrillation	48%	28%	0.028	22%	34%	0.457
Time to door (min)	71 ± 37	82 ± 43	0.128	64 ± 41	80 ± 42	0.256
NIHSS admission	15.3 ± 4.7	13.4 ± 5.9	0.061	16.2 ± 4.2	13.8 ± 5.7	0.129
Time to needle (min)	158 ± 49	159 ± 55	0.913	147 ± 47	160 ± 54	0.504
Length of stay	25 ± 25	20 ± 27	0.385	38 ± 49	20 ± 24	0.059
No occlusion	8%	18%	0.103	11%	16%	0.714
M1/ICA/BA occlusion	63%	56%	0.168	56%	48%	0.651
Hematological indices						
Admission lymphocyte	1.96 ± 0.97	2.21 ± 1.06	0.189	1.42 ± 0.58	2.19 ± 1.05	0.032
Admission neutrophil	6.57 ± 3.74	5.47 ± 2.41	0.039	8.04 ± 3.23	5.62 ± 2.79	0.014
Admission NLR	4.74 ± 5.29	3.15 ± 2.58	0.018	7.6 ± 7.39	3.33 ± 3.07	<0.001
Admission WBC	9.55 ± 3.7	8.55 ± 2.51	0.066	10.43 ± 3.29	8.72 ± 2.86	0.088
Admission hematocrit	39.91 ± 5.25	40.34 ± 4.56	0.622	37.64 ± 8.32	40.39 ± 4.4	0.092
Admission hemoglobin	13.32 ± 1.8	13.5 ± 1.68	0.580	12.38 ± 2.85	13.52 ± 1.6	0.052
Admission monocyte	0.66 ± 0.31	0.66 ± 0.25	0.966	0.69 ± 0.42	0.65 ± 0.26	0.704
Post-tPA lymphocyte	1.22 ± 0.67	1.61 ± 0.68	0.003	0.73 ± 0.39	1.55 ± 0.68	0.001
Post-tPA neutrophil	9.33 ± 4.48	6.68 ± 2.77	<0.001	13.63 ± 4.6	7.01 ± 3.04	<0.001
Post-tPA NLR	11.6 ± 12.44	5.3 ± 4.14	<0.001	26.2 ± 18.56	5.78 ± 4.47	<0.001
Post-tPA WBC	11.64 ± 4.42	9.2 ± 3.05	<0.001	15.17 ± 4.78	9.53 ± 3.28	<0.001
Post-tPA hematocrit	39.04 ± 4.89	38.96 ± 4.61	0.930	36.82 ± 6.67	39.13 ± 4.5	0.153
Post-tPAhemoglobin	13.03 ± 1.67	12.9 ± 2.06	0.724	12.16 ± 2.11	12.98 ± 1.94	0.218
Post-tPA monocyte	0.6 ± 0.32	0.65 ± 0.26	0.328	0.6 ± 0.27	0.64 ± 0.28	0.705

Abbreviations: BA, Basilar artery; BMI, Body mass index; ICA, internal carotid artery; IV, Intravenous; M1, the first segment of the middle cerebral artery (MCA); min, minute; NIHSS, National Institute of Health Stroke Scale; NLR, Neutrophil-to-Lymphocyte ratio; PH2, Parenchymal Hemorrhage type 2; tPA, recombinant tissue plasminogen activator; WBC, White blood cell.

variable degrees of accuracy. We herein briefly discuss the possible causes and consequences of these observations.

There may be many possible causes of NLR increase in the hyperacute ischemic stroke setting. The first, and probably the most decisive one, is the stroke-related acute stress reaction or hypercortisolism resulting in lymphopenia-neutrophilia response.[18] Lymphopenia reflecting stroke-mediated immune-depression plus neutrophilia reflecting early infection may contribute to NLR elevation, as well.

Determination, and perhaps monitoring, of NLR may be a useful parameter in stroke clinical practice.

Our study documents that NLR does not give dependable information about early tPA effectiveness, tPA-induced symptomatic cerebral hemorrhage, and long-term unfavorable prognosis during the first hours after stroke onset. Therefore, NLR has no role in patient selection for IV tPA. But, several previous studies[7,9] found that not direct NLR but high leukocyte/neutrophil count before tPA bolus showed an inverse correlation with chance of early recovery after tPA. In 1 study,[9] albeit not as an independent predictor, a positive linkage of the NLR increase with NIHSS reduction over the first 24 hour after tPA was noted. We herein found only a nonsignificant trend of positive association between early positive response and low NLR or neutrophil count obtained before tPA bolus. But, we failed to define a dependable threshold for tPA effectiveness and ineffectiveness. Thus, we do not suggest using pre-tPA CBC profile to triage patients to IV tPA or to thrombectomy.

Our results indicate that 24th hour NLR has stronger connections with prognosis and complications. It is important to note that NLR elevation develops after most of the tPA effect (response or bleeding) has already occurred. Therefore, it has much more importance during follow-up. Higher NLR points greater stress response, heavier clinical picture (as evidenced with high correlation with NIHSS as herein documented), larger infarct tissue, and worse prognosis. NLR increase becomes very pronounced when tPA-related cerebral bleeding occurs, as replicated in our study. This is another contributor of poor prognosis. However, it is difficult to suggest a direct role, or specificity, of increase of NLR in this serious adverse effect of tPA because similar connection was reported in hemorrhages observed in tPA-naïve atrial fibrillation-associated strokes[19] or those treated with

Table 4. *Accuracy of NLR in prediction of neurological outcomes*

	Threshold	AUC(95%CI)	Sensitivity, %	Specificity, %	*P*	Comment
A. Pre IV tPA Bolus						
tPA effectiveness	2.3	0.615 (0.530-0.696)	53.4	66.2	0.0150	Failed
tPA dramatic response	3.2	0.594 (0.508-0.676)	84	39.8	0.0726	Failed
3-month mRS >1	4.1	0.576 (0.490-0.659)	87	29.5	0.1323	Failed
3-month mRS >2	4.2	0.538 (0.452-0.622)	83	27.6	0.4331	Failed
Any hemorrhage	2.9	0.611 (0.525-0.691)	55	67	0.0410	Failed
PH type 2	2.9	0.809 (0.735-0.809)	89	63.9	0.0005	Fair
B. 24 hour						
tPA effectiveness	3.2	0.710 (0.628-0.783)	48	84	0.0001	Poor
tPA dramatic response	6.3	0.684 (0.601-0760)	89.5	45	0.0001	Poor
3-month mRS >1	3.6	0.737 (0.656-0.807)	65	73	0.0001	Poor
3-month mRS >2	3.6	0.728 (0.647-0.800)	62	79	0.0001	Poor
Any hemorrhage	5.9	0.722 (0.640-0.794)	67.5	72.5	0.0001	Poor
PH type 2	7.4	0.931 (0.877-0.967)	100	76	0.0001	Good

thrombectomy.[11] Again, at this point, it would not be wrong to say that NLR reflects an increased stress response along with increased sympathetic activity due to hematoma. The other factor linking elevated NLR to poor prognosis is infection. It was documented that increased NLR and lymphopenia with or without neutrophilia are linked to stroke-associated pneumonia.[20]

As all being post-priori (24th hour) cut-offs, we show that NLR ≤3.2 indicates IV tPA effectiveness, ≤3.6 favorable prognosis, and ≤7.4 absence of symptomatic cerebral hemorrhage. These are all predictors with low-to-moderate strength (Table 4) showing slight differences form those thresholds reported in the germane literature, such as NLR ≥ 4.8 being linked to symptomatic cerebral hemorrhage risk[7] and NLR ≤ 2.2 being linked to excellent response.[8]

We should mention some limitations regarding our study. The retrospective nature of the study is a significant limitation resulting exclusion of some patients. The number of patients is not enough to perform subgroup analyses. Data on the presence of infection and their parameters were not collected. Still, our study provided valuable findings. First, NLR was not elevated in the hyperacute period particularly before tPA bolus (4.5 hours). Therefore, NLR cannot be a criterion for scheduling the patient to thrombectomy by thinking of no benefit from tPA. Second, pronounced NLR elevations occur later and mostly in the patients with severe neurological deficit. NLR reaches to very high values after tPA associated cerebral hemorrhage develops. NLR refers to worse prognosis in this period as an epiphenomenon. Finally, it is currently not clear whether this rise is the cause or consequence of the clinical worsening. But, it could still be a target for monitoring of treatment goals.

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