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, 5: 367-373
pii: S0003469X18028452
Epub Ahead of Print 25 June 2018
free reading: www.annitalchir.com

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The effects of neutrophil to lymphocyte and platelet to lymphocyte ratios on prognosis in patients undergoing mechanical thrombectomy for acute ischemic stroke

INTRODUCTION: *The aim of the study was to investigate the effect of neutrophil lymphocyte (NLR) and platelet lymphocyte ratio (PLR) on prognosis in acute ischemic stroke (AIS) patients undergoing mechanical thrombectomy.*
MATERIAL-METHOD: *A retrospective study was made of the data of 56 patients aged 20-80 years who were diagnosed with AIS and underwent mechanical thrombectomy. Thrombolysis in Brain Ischemia (TIBI) status was evaluated with transcranial Doppler after treatment. The National Institutes of Health Stroke Scale (NIHHS) and modified Rankin scale (mRS) were used to indicate neurological and functional deficits.*
RESULTS: *No difference was determined in the NLR and PLR between patients with or without middle cerebral artery (MCA) occlusion, T and basilar occlusion. These ratios were also no different between the groups with different degrees of recanalization. Platelet lymphocyte ratio was lower in patients with a dramatic improvement at the 24th hour (p=0.046). Neutrophil lymphocyte ratio was higher in patients with symptomatic hemorrhage (p=0.046).*
CONCLUSION: *Although no relationship with outcome has yet been shown, the association with hemorrhagic change and the recovery parameters at the 24th hour may enable NLR and PLR to be used as significant prognostic factors in patients with acute ischemic stroke undergoing mechanical thrombectomy. Further studies are needed.*

KEY WORDS: Ischemia, Mechanical thrombectomy, Neutrophil lymphocyte ratio, Platelet lymphocyte ratio, Stroke

Introduction

Stroke, previously known as cerebrovascular event (CVE) or stroke syndrome, is a neuronal dysfunction and non-specific brain damage resulting from loss of energy support and focal tissue oxygenation due to many pathophysiological mechanisms. In ICD-10-CM published in 2015 (The International Classification of Diseases 10th revision, together with clinical modification), cerebrovascular diseases were divided into several categories: transient ischemic attack (TIA), cerebral infarction, intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and infarct associated with cerebral thrombosis. Of all strokes, 87% are ischemic stroke, 10% are intracerebral hemorrhage and 3% are subarachnoid hemorrhage [1]. Acute ischemic stroke (AIS) is characterized by a sudden loss of blood flow in an area of the brain and the resulting loss of neurological function in the affected area.

Thrombolytic therapy is currently widely used for acute ischemic stroke in appropriate patients. The efficacy and complications of intravenous fibrinolytics in the treatment of acute ischemic stroke have been revealed in many studies. Intra-arterial fibrinolytics can be used alone or with intravenous fibrinolytics. In many recent, ran-

Pervenuto in Redazione Aprile 2018. Accettato per la pubblicazione Febbraio 2018.
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domized, clinical studies, mechanical thrombectomy has been shown to provide revascularization. Mechanical thrombectomy can be performed in patients with high INR values because of the use of oral anticoagulants and in those who have not responded sufficiently to fibrinolytic therapy [2,3].

Atherosclerosis of the cerebral arteries, which plays an important role in the development of acute ischemic stroke, is a diffuse inflammatory and degenerative process resulting in the formation of plaque that involves arteries and is seen more intensely in certain arteries. Immune dysregulation plays an important role in the response to acute ischemic stroke [4-6].

Inflammatory cells vary according to the stage and intensity of the inflammation. The cytokine pool in the environment determines cell diversity involved in inflammation. Some clinical studies have been carried out in the belief that NLR and PLR, as indicators of this response, may also contribute to the prognosis of acute ischemic stroke. However, very few studies have investigated the effect of NLR on prognosis in patients who have undergone mechanical thrombectomy. This study aimed to investigate the effects of NLR and PLR on prognosis in patients who presented at hospital with acute ischemic stroke and underwent mechanical thrombectomy.

Material and Method

The study included 56 adult patients, aged 20-80 years, who presented at the medical faculties of Gaziantep University and Ba kent University and were diagnosed with acute ischemic stroke (AIS) and then underwent mechanical thrombectomy between 2014 and 2015. The inclusion criteria were that patients presented within the first 6 hours from the onset of stroke symptoms arising from an anterior circulatory disorder; patients presented within the first 8 hours from the onset of basilar thrombosis; patients with NIHSS≥10 at the beginning of intravenous rt-PA and no clinical improvement after rt-PA; and patients with contraindication for intravenous rt-PA and NIHSS≥10 at the time of presentation. Exclusion criteria were moderate-to-severe stroke patients with dramatic clinical improvement (NIHSS≥8) following intravenous rt-PA, patients with pre-existing neurological disease leading to moderate disability (mRS≥2), patients with advanced and terminal diseases, and patients with suspected bacterial endocarditis or septic emboli. The data of patients included in the study were reviewed retrospectively.

Complete blood cell counts of the patients were performed with the Sysmexxn 9000 device. The neutrophil lymphocyte ratio (NLR) was calculated by dividing the number of neutrophils by the number of lymphocytes. The platelet lymphocyte ratio (PLR) was obtained by dividing the number of platelets by the number of lymphocytes.

Digital subtraction angiography (DSA) was performed to determine the location of the occluded vessels in AIS patients. The Thrombolysis in Brain Ischemia (TIBI) status was evaluated using transcranial Doppler ultrasound imaging to analyze the blood flow following the treatment.

The National Institutes of Health Stroke Scale (NIHSS) scores were used as a quantitative indicator of stroke-related neurological deficit in the application, during the acute evaluations at the 24th hour, and in the 3rd month following admission. The modified Rankin scale (mRS) was used to make a functional evaluation of the neurological disability of the patients.

Statistical analyses of the study data were performed using SPSS 22.0 (IBM Corporation, Armonk, New York, United States) software. The Independent-Samples T test was used with Bootstrap results, while the Mann-Whitney U test was used with the Monte Carlo results when comparing two independent groups in respect of quantitative results. The Kruskal-Wallis H Test, as a non-parametric method, was used together with the Monte Carlo results when comparing more than two groups quantitatively. Quantitative variables were stated as mean±standard deviation (SD) and median range (Minimum-Maximum), and categorical variables were stated as number (n) and percentage (%) in the tables. The variables were analyzed at 95% confidence level and a value of $p<0.05$ was accepted as statistically significant.

Results

Of the total 56 patients in the study, 21 were female and the mean age was 58.23 ± 11.94 years. The DSA results showed 8.9% normal, 28.6% middle cerebral artery (MCA) root occlusion, 21.4% distal MCA occlusion and 19.6% basilar artery occlusion. Following the treatment, 58.9% complete recanalization was determined in TIBI. Flow was determined in 12.5% of patients as >50% flow, 17.9% had <50% flow and 10.7% had no flow. Fisher type 1 petechial hemorrhagic transformation developed in 42.9% of the patients. The mortality rate was determined as 41.1% of the total group (Table I).

The blood counts of the patients are shown in Table II. The mean NLR and PLR were calculated as 9.80±21.45 and 29.95±57.15 respectively (Table II).

The relationship between the clinical findings of the patients and NLR and PLR is shown in Table III. According to the DSA findings, there was no difference between patients determined with MCA occlusion (distal or root), T occlusion, basilar occlusion and patients without occlusion in term of NLR or PLR. In TIBI, there was no significant relationship between the groups with different recanalization rates in terms of NLR and PLR (Table III).

The PLR was found to be 10.22 in the patients with

TABLE I - *The clinical and imaging findings of the patients.*

Clinical and imaging findings		Age (years)		
		n	Mean±SD.	Maximum-Minimum
Female		21	56.0±13.36	74-35
Male		35	59.6±10.99	78-38
Total		56	58.23±11.94	78-35
			n	%
Gender	Female		21	37.5
	Male		35	62.5
Diabetes	Absent		40	71.4
	Present		16	28.6
Hypertension	Absent		20	35.7
	Present		36	64.3
Smoking	Absent		41	73.2
	Present		15	26.8
CRF	Absent		47	83.9
	Present		9	16.1
Hyperlipidemia	Absent		33	58.9
	Present		23	41.1
Coronary artery disease	Absent		28	50.0
	Present		28	50.0
AF	Absent		43	76.8
	Present		13	23.2
DSA	normal		5	8.9
	MCA root occlusion		16	28.6
	MCA distal occlusion		12	21.4
	Carotid T occlusion		12	21.4
	basilar a. occlusion		11	19.6
TIBI	No flow		6	10.7
	< 50% flow		10	17.9
	> 50% flow		7	12.5
	Complete recanalization		33	58.9
Hemorrhagic transformation according to Fisher classification	Absent		32	57.1
	Type I Petechial hemorrhage		24	42.9
Mortality	Absent		33	58.9
	Present		23	41.1

AF: Atrial fibrillation, Carotid T occlusion: Occlusion of the carotid artery, middle and anterior cerebral artery.CRF: Chronic renal failure, MCA: Middle cerebral artery TIBI: Thrombolysis in Brain Ischemia.

TABLE II - *The evaluation of blood count and stroke scores of the patients.*

	Mean±SD.	Median	Maximum-Minimum
Platelet	275.32±227.86	244	1883-115
Lymphocyte	18.09±13.68	15.61	70.6-0.59
Neutrophil	74.80±14.27	77.65	94.4-25.5
Neutrophil Lymphocyte Ratio	9.80±21.45	5.06	160-0.36
Platelet Lymphocyte Ratio	29.95±57.15	16.62	420.34-4.99
NIHSS admission	16.09±3.33	16	23-7
NIHSS 24th hour	13.36±6.55	14	23-1
NIHSS 3rd month	3.64±4.32	2	16-0
mRS 3rd month	4.09±1.89	4	6-1

dramatic improvement in the 24th hour, which was significantly lower than those without improvement (p=0.046) (Fig. 1). The NLR was 7.96 in the group of patients with symptomatic hemorrhage, which was significantly higher than in those without (p=0.046) (Fig. 2). There was no relationship between other outcomes in the clinical features of the patients and NLR or PLR (Table IV).

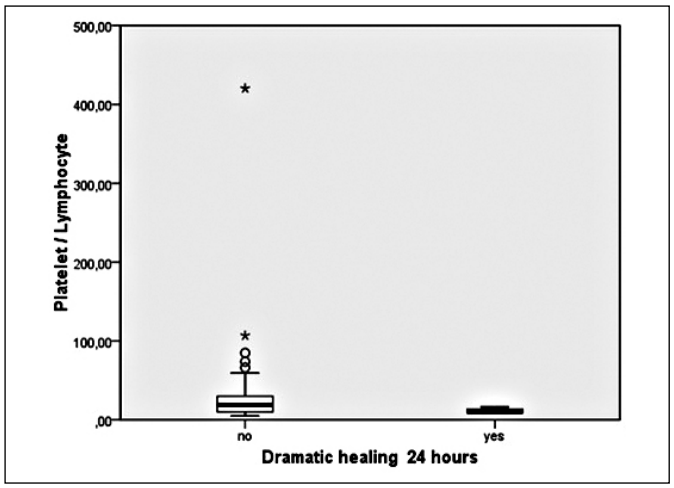

Fig. 1: Relationships between dramatic recovery and PLR.

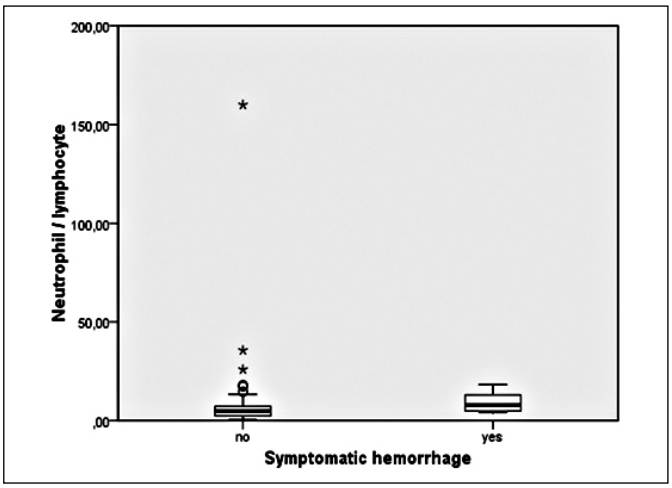

Fig. 2: Relationships between symptomatic hemorrhage and PLR.

TABLE III - *Comparison of NLR and PLR with the clinical findings of the patients.*

N=56	Neutrophil Lymphocyte Ratio Median (Max.-Min.)	P Value	Platelet Lymphocyte Ratio Median (Max.-Min.)	P Value
Gender				
Female	5.81 (25.92-1.68)	0.249	19.87 (84.84-5.12)	0.203
Male	4.40 (160.00-0.36)		13.92 (420.34-4.99)	
Diabetes				
Absent	4.94 (160.00-1.42)	0.455	16.61 (420.34-5.12)	0.638
Present	6.01 (18.26-0.36)		17.86 (66.28-4.99)	
Hypertension				
Absent	4.75 (160.00-1.68)	0.824	15.12 (420.34-5.12)	0.695
Present	5.29 (18.26-0.36)		18.70 (73.76-4.99)	
Smoking				
Absent	5.61 (35.61-0.36)	0.152	18.03 (106.82-4.99)	0.424
Present	4.09 (160.00-1.42)		13.92 (420.34-5.38)	
CRF				
Absent	5.10 (160.00-1.42)	0.583	17.15 (420.34-5.12)	0.306
Present	5.02 (18.26-0.36)		12.95 (66.28-4.99)	
Hyperlipidemia				
Absent	5.55 (160.00-0.36)	0.309	16.35 (420.34-4.99)	0.357
Present	4.95 (17.71-0.36)		17.15 (66.28-4.99)	
Coronary artery disease				
Absent	5.87 (160.00-1.68)	0.100	18.10 (420.34-5.12)	0.247
Present	4.20 (18.26-0.36)		14.97 (73.76-4.99)	
AF				
Absent	5.10 (160.00-0.36)	0.968	16.90 (420.34-4.99)	0.714
Present	4.31 (18.26-1.68)		16.35 (73.76-5.12)	
DSA				
normal	4.31 (8.19-2.17)	0.117	12.70 (23.30-6.90)	0.310
MCA root occlusion	5.84 (25.92-1.88)		21.31 (84.84-5.38)	
MCA distal occlusion	3.08 (12.99-1.42)		9.27 (73.76-6.09)	
T occlusion	6.01 (11.44-2.46)		17.59 (47.81-7.80)	
basilar occlusion	6.48 (160.00-0.36)		13.92 (420.34-4.99)	
TIBI				
Absent	13.20 (18.00-2.23)	0.508	26.43 (47.81-7.49)	0.651
Less than 50% flow	4.62 (25.92-1.42)		17.59 (84.84-5.38)	
More than 50% flow	6.32 (160.00-2.17)		19.87 (420.34-6.90)	
Completely recanalized	5.02 (35.61-0.36)		13.92 (106.82-4.99)	
Hemorrhagic Transformation				
Absent	5.33 (160.00-1.68)	0.628	16.62 (420.34-5.12)	0.787
Type I Petechial Hemorrhage	4.65 (25.92-0.36)		16.42 (84.84-4.99)	
Mortality				
Absent	4.34 (25.92-1.68)	0.177	16.33 (84.84-5.12)	0.498
Present	6.48 (160.00-0.36)		19.37 (420.34-4.99)	

TABLE IV - *Relationship of NLR and PLR with the clinical changes of the patients.*

N=56	Neutrophil Lymphocyte Ratio Median (Max.-Min.)	P Value	Platelet Lymphocyte Ratio Median (Max.-Min.)	P Value
Dramatic recovery 24				
Absent	5.71 (160.00-0.36)	0.104	18.79 (420.34-4.99)	0.046
Present	3.64 (7.08-2.17)		10.22 (16.33-8.48)	
Recovery24				
Absent	6.48 (160.00-0.36)	0.056	19.87 (420.34-4.99)	0.103
Present	4.31 (8.19-1.68)		13.59 (73.76-5.12)	
Deterioration 24				
Absent	5.02 (35.61-0.36)	0.328	15.08 (106.82-4.99)	0.312
Present	7.35 (160.00-0.36)		19.87 (420.34-4.99)	
Symptomatic hemorrhage				
Absent	4.92 (160.00-0.36)	0.046	16.33 (420.34-4.99)	0.172
Present	7.96 (18.26-4.23)		22.26 (66.28-7.80)	
Very good outcome				
Absent	5.29 (160.00-0.36)	0.689	18.15 (420.34-4.99)	0.291
Present	4.63 (7.12-2.17)		13.47 (16.90-8.70)	
Good outcome				
Absent	5.71 (160.00-0.36)	0.303	18.15 (420.34-4.99)	0.611
Present	4.59 (8.19-2.17)		14.34 (73.76-8.48)	

Mann Whitney U Test (Monte Carlo) - Max.:Maximum - Min.: Minimum

TABLE V - *Relationships between neurological defect and disability scores and NLR and PLR*

	NLR r	NLR P Value	PLR r	PLR P Value
NIHSS admission	0.141	0.308	0.120	0.387
NIHSS 24th hour	0.250	0.069	0.249	0.070
NIHSS 3rd month	-0.174	0.209	-0.170	0.219
mRS 3rd month	0.244	0.076	0.226	0.101

Partial Correlation Test - Age and gender adjusted

A statistically insignificant positive correlation was determined between the NIHSS scores and NLR and PLR values at the time of admission and at the 24th hour. A statistically insignificant negative correlation was found between NLR (r=-0.174) and PLR (r =-0.170) and NIHSS score in the 3rd month (Table V).

Discussion

In the management of an acute ischemic stroke (AIS) patient, restoration of the blood flow in the hyperacute phase is ensured once the medical stability of the patient is established and other medical conditions contributing to the patient's symptoms have been taken into account [7]. Intra-arterial mechanical thrombectomies can be performed using stent retrievers in centers experienced in acute ischemic stroke syndrome when it has been caused by a large arterial occlusion in the anterior circulation, in cases where hemorrhage is excluded and there are no or minimal ischemic findings on CT within the first 6 hours of stroke onset.

Five multicenter randomized controlled trials (MR CLEAN, ESCAPE, SWIFT PRIME, EXTEND-IA and REVASCAT) have shown that early intra-arterial therapy with second generation mechanical thrombectomy devices is superior to intravenous fibrinolysis in the treatment of ischemic stroke caused by occlusion of the major arteries in the proximal anterior circulation (8-12). In the meta-analysis of these studies, that the mechanical thrombectomy significantly decreased disability was demonstrated by a drop of 1 or more scores in the mRS on the 90th day (OR 2.49. 95% confidence interval 1.76-3.53). Mechanical thrombectomy is useful in severe stroke syndromes, including patients aged ≥80 years, who are not treated with intravenous fibrinolytics.

In acute ischemic stroke patients, there are other factors that have a significant effect on prognosis other than recanalization. Basal NIHSS≤10, lower mean arterial pressure, ≤85 years of age and the absence of specific abnormalities on CT are factors that improve the prognosis [13,14]. Recent studies of NLR, a marker of subclinical inflammation, have suggested that NLR may be a predictor of cardiovascular disease, sepsis, metabolic syndrome, and cancer, and may also be an indicator of in-hospital morbidity and mortality [15-17]. High NLR in stroke patients has been associated with arginase 1 (ARG1) released from neutrophils. Several studies have

been performed on the effect of ARG1 on stroke [18-20]. NLR has been shown to be an important predictor of 60-day mortality following acute ischemic stroke [21]. Similarly, several studies have shown a relationship between PLR, a new and simple indicator that can be used as a marker of inflammation, and prognosis in patients with coronary artery disease, acute coronary syndrome and acute ischemic stroke [22,23]. As yet there is no biomarker available that can be used extensively to predict the benefit of endovascular treatment in acute ischemic stroke. The NLR and PLR method is significant as it is an easy and inexpensive method that can be performed with a routine blood count.

Brooks et al. performed a study of 116 patients diagnosed with acute ischemic stroke [24]. Three different endovascular treatment methods were applied to the patients: iv-tPA, intraarterial (IA) tPA and mechanical thrombectomy (MT). A significant positive correlation was shown between the NLR and NIHSS scores when the relationship between the stroke scores and the NLR of these patients was analyzed (r=0.38; p<0.0001). In the current study, there was no significant difference in NLR and PLR between the groups with mRS 0-1 (very good outcome) and mRS 0-2 (good outcome). In addition, there was no significant correlation between 3rd month mRS scores and NLR or PLR. In the study by Brooks et al., a significant positive correlation was determined between NLR and outcome (r=0.24. p=0.018). NLR ≥5.9 was determined as the cutoff value in terms of poor outcome (mRS 4-6). NLR ≤3.2 was found to be an important limit in terms of functional independence. When the mRS was classified in two groups as scores of 0-3 and 4-6, NLR was shown to be a strong predictor of functional independence. In the current study, no significant difference was found in the TIBI recanalization groups in terms of NLR and PLR.

In a study by Tokgöz et al. of 1351 acute ischemic stroke patients, NLR was shown to be moderately correlated with NIHSS (r=5.44. P=0.001) and higher in the group with mortality (38). In this study, there was no correlation between NIHSS at 0, 24th hour and 3rd month scores and NLR or PLR. NLR was significantly higher in the group of patients with symptomatic hemorrhage than in those without improvement. In another study by Tokgöz et al. of 255 patients with acute ischemic stroke (supratentorial infarct), the cut-off value of NLR and its place in predicting the prognosis in patients who did not undergo interventional treatment were investigated [21]. A strong and positive correlation was determined between NIHSS score and NLR (r= 0.64; p<0.001). In all subtypes, the NLR values were higher in deceased groups. The main finding of that study was that NLR predicted the short-term mortality of acute ischemic stroke independently of other factors.

A stronger association was found between NLR and outcome in the current study patients aged <80 years compared to patients aged >80 years, which has been associated with the decrease in neutrophil percentage, chemotaxis, phagocytosis and cytokine release with increasing age [25]. Independent of any intervention, the fact that NLR helps to predict the outcome shows that NLR could be used to determine patients to be included in clinical trials. However, as with the present study, there is a need for studies including patients who have undergone MT.

In the present study, there was no statistically significant difference between the TIBI groups in terms of PLR. However, in this study, it was shown that patients who underwent mTICI (modified treatment in cerebral ischemia), i.e. successful revascularization, were more likely to be in the low PLR group (p=0.015). Better functional outcomes (mRS≤2) were determined in the low PLR group (p =0.004 1st month; p = 0.014 3rd month respectively). In conclusion, it was shown that high PLR is associated with poor recanalization, poor prognosis, and large infarct area.

Conclusion

In this study, it was shown that NLR and PLR did not correlate with all outcome parameters in acute ischemic stroke patients who underwent mechanical thrombectomy, although PLR was lower in the group with a dramatic improvement in the 24th hour. Despite studies in literature which have shown the relationship between NLR and outcome in acute ischemic stroke patients, there has been very limited research that has included patients undergoing mechanical thrombectomy. As NLR determined at the time of admission has a predictive effect on the benefit to be seen by patients of the treatment they undergo, there is a need for further studies of the management of treatment with NLR.

Riassunto

Ricerca sull'effetto del rapporto neutrofili/linfociti (NLR) e di quello piastrine/linfociti (PLR) sulla prognosi dell'ictus ischemico acuto in pazienti sottoposti a trombectomia meccanica.

Si tratta di uno studio retrospettivo sui dati di 56 pazienti dell'arco di età da 20 a 80 anni con ictus ischemico acuto sottoposti a trombectomia meccanica. Lo stato della trombolisi dell'ischemia cerebrale è stata valutata mediante Doppler transcranico dopo il trattamento, e per indicare i deficit neurologici e funzionali sono stati impiegati la Scala del National Institutes of Health Stroke (NIHHS) e quella modificata di Rankin (mRS). Non è stata rilevata nessuna differenza trai due rapporti nei pazienti con occlusione o meno dell'arteria cerebrale media (MCA), trombosi e occlusione del tronco basilare. I rapporti non erano parimenti differenti tra i gruppi con differenti gradi di ricanalizzazione. Il rapporto

piastrine-linfociti risulta inferiore nei pazienti con miglioramento rilevante entro la 24° ora (p=0,046). Il rapporto neutrofili-linfociti risulta maggiore nei pazienti con emorragia sintomatica (p=0,046).
In conclusione sebbene non sia ancora stata mostrata una correlazione con l'esito, l'associazione con dell'ischemia con l'emorragia ed i parametri del recupero alla 24° ora possono convalidate i rapporti NLR e PLR quale significativo indice prognostico in questo tipo di pazienti. Sono necessari ulteriori studi.

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