High Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio are Associated with Symptomatic Internal Carotid Artery Stenosis

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Introduction: The neutrophil to lymphocyte ratio (NLR) and the platelet to lymphocyte ratio (PLR) have been identified as predictive factors in several cardiovascular diseases but their significance in patients with internal carotid artery (ICA) stenosis is still poorly known. The aim of this study was to determine the clinical significance of the preoperative NLR and PLR in patients with ICA stenosis undergoing carotid endarterectomy. *Material and Methods:* Consecutive patients who underwent carotid endarterectomy for ICA stenosis were retrospectively included (n = 270). The population was divided into 2 series of 4 groups based on the quartile values of the preoperative NLR and PLR: group Ia (NLR < 1.5), IIa (1.50 < NLR < 2.07), IIIa (2.07 < NLR < 2.95), IVa (NLR>2.95), and group Ib (PLR < 86.6), IIb (86.6 < PLR < 111.7), IIIb (111.7 < PLR < 148.3), IVb (PLR > 148.3). Clinical characteristics and 30-day postoperative outcomes were compared among the groups. *Results:* One death (.4%) was reported during the 30-day postoperative period and the overall stroke and death rate was 1.5%. The proportion of patients with symptomatic ICA stenosis were significantly higher in group IVa compared to groups Ia, IIa, IIIa (64.2% vs 33.8%, 44.8% and 45.6%, respectively, $P = .005$), and higher in group IVb compared to groups Ib, IIb, IIIb (59.7% vs 47.1%, 35.8%, 45.6%, $P = .051$). No significant difference on 30-day postoperative all-cause complications was observed among the groups. *Conclusions:* A high preoperative NLR and PLR is significantly associated with symptomatic ICA stenosis. Further studies are required to determine their interest as predictors of postoperative outcomes in patients undergoing carotid endarterectomy.

Key Words: Internal carotid artery stenosis—neutrophil to lymphocyte ratio—platelet to lymphocyte ratio—white blood count

Introduction

Internal carotid artery (ICA) stenosis is a major cause of stroke[1,2] and its curative treatment relies on surgical approaches among which carotid endarterectomy is one of the most commonly used.[3-6] Atherosclerosis represents a leading cause of ICA stenosis and is associated with systemic inflammation.[7,8] As a consequence, several circulating inflammatory proteins such as C-reactive protein or interleukin-6 (IL-6) have been identified as reliable

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biomarkers of carotid atherosclerosis[9] and the interest of white blood count as a predictive marker has been addressed in several cardiovascular diseases.[10,11] Specifically, the usefulness of the neutrophil to lymphocyte (NLR) and platelet to lymphocyte (PLR) ratio has been investigated in patients with coronary artery disease, myocardial infarction, aortic aneurysm, and in context of major vascular surgery.[12-17] NLR and PLR have been identified as prognostic predictors of stroke.[18,19] However, the link between NLR and PLR in context of ICA stenosis surgical repair has been so far poorly explored. The aim of this study was to determine the clinical significance of the preoperative NLR and PLR in patients with ICA stenosis undergoing carotid endarterectomy.

Material and Methods

Patients

Consecutive patients who underwent carotid endarterectomy for ICA stenosis were retrospectively included in the Department of Vascular Surgery at the University Hospital of Nice between January 2015 and December 2017. The study was approved by our local ethic committee. The study exclusion criteria included history of hematologic and systemic inflammatory diseases. Clinical preoperative characteristics were collected and included age, sex, and the presence of cardiovascular risk factors. The preoperative white blood count was collected and the NLR and PLR were calculated by dividing the absolute value of neutrophils to lymphocytes and platelets to lymphocytes, respectively. ICA stenosis was defined as a stenosis of the extra cranial portion of the ICA and the degree of stenosis was measured by Doppler ultrasound associated with injected CT scan or MRI according to the North American Symptomatic Carotid Endarterectomy Trial.[20] Symptomatic ICA stenosis was defined as a history of transient ischemic attack, stroke affecting the corresponding territory or amaurosis fugax within the previous 6 months.[21] Carotid endarterectomy was performed under general anesthesia using eversion, patch, or bypass technique depending on patient's anatomic characteristics.

Data Collection

Clinical data and procedural characteristics were collected using electronic and manuscript medical records, as well as a computer software program named Clinicom. Imaging data were recorded and extracted from the software Picture Archiving and Communication System. Postprocessing analysis was performed using the Aquarius workstation (TeraRecon, Inc. San Mateo).

Study End Points

To investigate the clinical significance of the preoperative NLR and PLR, the population was divided into 4 groups based on the quartile values of the NLR and PLR, respectively. Clinical characteristics and 30-day postoperative outcomes were compared among the groups. The 30-day all-cause mortality was recorded. Postoperative complications were defined as any life-threatening event requiring the need of a therapy or any complications leading to disability or death. They were classified based on clinical symptomatology. Neurologic complications included cranial nerve injury, convulsions, and the occurrence of stroke or transient ischemic attack. Stroke and transient ischemic attack were defined as the occurrence of clinical symptoms affecting the corresponding territory. Ischemic and hemorrhagic stroke were diagnosed based on Magnetic Resonance Imaging. Cardiac complications included myocardial infarction (diagnosed based on the electrocardiogram data associated with an elevation of troponin) and rhythm disturbance. Vascular complications included hematoma and external carotid thrombosis.

Statistical Analysis

Categorical data were expressed as the number of patients and percentage and continuous variables were expressed as the mean ± standard deviation. Group differences were compared using a chi-square test for categorical data and a 1-way analysis of variance for continuous variables. Correlations were determined by Pearson's correlation coefficient. A 2-tailed P value <.05 was considered as significant. Statistical analyses were performed using GraphPad Prism software (version 7.00, La Jolla, CA).

Results

Clinical Characteristics and Postoperative Outcome According to the Preoperative NLR

In total, 270 patients with ICA stenosis who underwent carotid endarterectomy were included. The population was divided into 4 groups based on the preoperative NLR value: group Ia (NLR < 1.5), group IIa (1.50 < NLR < 2.07), group IIIa (2.07 < NLR < 2.95), and group IVa (NLR > 2.95); Table 1). Patients from group IVa had significantly higher leukocyte and neutrophil count, with lower lymphocyte count compared to the other groups (P < .001). Hemoglobin was significantly lower in patients from group IVa (13.3 g/dL vs 13.4, 14 and 14.1, P = .009). Patients from group IVa were significantly older than the other groups (75.1 years vs 69.4, 72.1 and 73.8, respectively, P = .006) and the proportion of men was higher. No significant difference was observed among the groups regarding the presence of cardiovascular risk factors. The proportion of patients with symptomatic ICA stenosis was significantly higher in group IVa compared to the other groups (64.2% vs 33.8%, 44.8% and 45.6%, respectively, P = .005). The degree of ICA stenosis was similar

Table 1. *Comparison of patients'' characteristics according to the NLR value*

Characteristics		Group Ia NLR < 1.50 (n = 68)	Group IIa 1.50 < NLR < 2.07 (n = 67)	Group IIIa 2.07 < NLR < 2.95 (n = 68)	Group IVa NLR > 2.95 (n= 67)	*P* value
General characteristics	Age	69.4 ±10.6	72.1 ±10.3	73.8 ±9.3	75.1 ±9.10	0.006
	Male sex	34 (50%)	45 (67.2%)	50 (73.5%)	49 (73.10%)	0.012
	Diabetes	17 (25%)	18 (26.9%)	16 (23.5%)	21 (31.30%)	0.755
	Arterial hypertension	46 (67.6%)	49 (73.1%)	49 (72.1%)	53 (79.10%)	0.515
	Dyslipidemia	24 (35.3%)	24 (35.8%)	32 (47.1%)	19 (28.40%)	0.156
	Smoking	21 (30.9%)	20 (29.9%)	20 (29.4%)	17 (25.40%)	0.902
	Atrial fibrillation	8 (11.8%)	5 (7.5%)	6 (8.8%)	5 (7.50%)	0.794
Clinical characteristics	Symptomatic ICA stenosis	23 (33.8%)	30 (44.8%)	31 (45.6%)	43 (64.20%)	0.005
	Degree of ICA stenosis (%)	75.9 ±10.4	74.7 ±9.9	75.4 ±10.3	73.50±10.40	0.598
Procedural characteristics	Carotid clamping time (min)	38.4 ±16.2	37.7 ±13.5	39.3 ±13	33.80±14	0.179
	Shunt	7 (10.3%)	2 (3%)	4 (5.9%)	4 (6%)	0.374
	Surgical technique					
	Patch	44 (64.7%)	42 (62.7%)	40 (58.8%)	32 (47.80%)	0.191
	Eversion	23 (33.8%)	25 (37.3%)	28 (41.2%)	35 (52.20%)	0.150
	Bypass	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0.395
Blood count	Leukocytes (*10^9 /L)	7.2 ±1.8	7.4 ±1.8	7.9 ±2.3	9.40±2.90	<0.0001
	Neutrophils (*10^9 /L)	3.4 ±0.90	4.2 ±1.1	4.9 ±1.4	7 ±2.70	<0.0001
	Lymphocytes (*10^9 /L)	2.9 ±0.80	2.3 ±0.6	1.9 ±0.6	1.50±0.50	<0.0001
	Monocytes (*10^9 /L)	0.70±1.0	0.7 ±0.6	0.8 ±0.9	0.80±0.30	0.950
	Platelets (*10^9 /L)	240.7 ±70.7	231 ±51.5	232 ±69.3	255.40±91.70	0.181
	Hemoglobin (g/ dL)	13.4 ±1.9	14 ±1.4	14.1 ±1.4	13.30±2.10	0.009
	NLR	1.19 ±0.24	1.82 ±0.17	2.53 ±0.26	5.36 ±2.96	<0.0001
30-day postoperative outcome	Mortality	0 (0%)	0 (0%)	0 (0%)	1 (1.50%)	0.386
	All-cause complications	5 (7.4%)	12 (17.9%)	8 (11.8%)	9 (13.40%)	0.320
	Neurologic complications	0 (0%)	3 (4.5%)	6 (8.8%)	3 (4.50%)	0.103
	TIA	0 (0%)	0 (0%)	2 (2.9%)	0 (0%)	0.112
	Ischemic stroke	0 (0%)	0 (0%)	0 (0%)	1 (1.50%)	0.392
	Hemorrhagic stroke	0 (0%)	0 (0%)	0 (0%)	1 (1.50%)	0.392
	Cranial nerve injury/ seizure	0 (0%)	3 (4.5%)	4 (5.9%)	1 (1.50%)	0.163
	Vascular complications	3 (4.4%)	4 (6%)	1 (1.5%)	3 (4.50%)	0.606
	Cardiac complications	1 (1.5%)	2 (3%)	1 (1.5%)	2 (3%)	0.870

Values are mean ±standard deviation or n (%). % are expressed compared to the groups (67- 68 patients).

Abbreviations: ICA, internal carotid artery;NA, not applicable;NLR, neutrophil to lymphocyte ratio;TIA, transient ischemic attack.

among the groups (75.9% vs 74.7%, 75.4% and 73.5%, P = .598) and the procedural characteristics did not significantly differ. In the whole cohort, one death (.4%) was reported during the 30-day postoperative period. The patient developed a postoperative hemorrhagic stroke and died 10 days after the surgery. The overall stroke and death rate was 1.5%. The 30-day postoperative outcome was similar among the groups with all-cause complications occurring in 7.4%, 17.9%, 11.8%, and 13.4% of patients, P = .320. No significant difference was observed regarding neurologic complications and stroke occurrence.

Clinical Characteristics and Postoperative Outcome According to the Preoperative PLR

The population was then divided into 4 groups based on the preoperative PLR: group Ib (PLR < 86.6), group IIb (86.6 < PLR < 111.7), group IIIb (111.7 < PLR < 148.3), and group IVb (PLR > 148.3; Table 2). Platelet count was significantly higher in group IVb compared to the others, and neutrophil count and hemoglobin concentration were lower. No significant difference regarding the presence of cardiovascular risk factors was observed. The surgical techniques used were similar but the mean carotid clamping time was significantly higher in group IIb compared to the others (42.4 minutes vs 37.3, 36.1, 33.4, P = .006). The degree of ICA stenosis did not significantly differ (74.9% vs 75.4%, 74.8%, and 74.3%, P = .948). The proportion of symptomatic ICA stenosis was significantly higher in patients from group IVb compared to the others (59.7% vs 47.1%, 35.8%, 45.6%, P = .051). The 30-day postoperative outcome was similar among the groups except the proportion of neurologic complications which was higher in group IIb compared to the others (11.9% vs 0%, 4.4% and 1.5%, P = .004). The rate of combined stroke and transient ischemic attack was higher in group IIb compared to the others (0% vs 6%, 0% and 0%, P = .006).

Correlation of Preoperative NLR and PLR with the Degree of ICA Stenosis

To further explore the link between the preoperative white blood count and the severity of ICA stenosis, the correlation between NLR and PLR and the degree of stenosis was investigated (Fig 1). The NLR and PLR did not directly correlate with the degree of ICA stenosis, as revealed by Pearson's coefficient correlation close to 0 (r = −.015, P = .816 and r = −.015, P = .805, respectively).

Discussion

The aim of this study was to investigate the clinical significance of the preoperative NLR and PLR in patients with ICA stenosis undergoing carotid endarterectomy. Our results show that high NLR and PLR are associated with symptomatic ICA stenosis. Several studies have addressed the link between NLR and ICA stenosis. A first study revealed that patients with high NLR had significantly higher prevalence of coronary artery disease and carotid artery atherosclerosis compared to those with a low NLR.[22] In addition, NLR has been identified as a strong predictor of the presence and number of carotid atherosclerotic plaques, suggesting its interest as a marker of the severity of the disease.[16] These findings are corroborated by other studies which found a significant positive association between NLR and carotid artery intima-media thickening.[23,24] In addition, NLR was associated with maximal and accumulated extracranial carotid stenosis.[25] Similarly to our results, a study found that a NLR value above 2.6 was an independent predictor for ICA stenosis to become symptomatic.[26] Interestingly, some investigators found a significant difference of NLR between patients with calcified plaques and those with noncalcified plaques, suggesting an association of NLR with plaque morphology.[27]

Inflammation is a key process in the pathogenesis of atherosclerosis.[28-30] Atherosclerosis is considered as a chronic inflammatory process that results from an interaction between modified lipoproteins, inflammatory cells, and constitutive cells of the arterial wall.[31] Carotid plaques are composed of lipid core associated with infiltration of inflammatory cells covered with a fibrous cap.[32] The progressive development of plaques protruding into the arterial lumen leads to the occurrence of stenosis and/or occlusions.[28] While a plaque can be stable and remain asymptomatic, it can also evolve to fissure or rupture due to active inflammation and generate arterial embolization.[32] The presence of plaques in the carotid artery exposes to the risk of transient ischemic attack and ischemic stroke. It is estimated that approximately 20% of ischemic strokes originate from carotid plaques, mainly due to arterio-arterial embolization.[33,34]

Neutrophils play a critical role in atherosclerosis and are involved in plaque rupture, reperfusion damage, and plaque remodeling.[35] Neutrophil count is associated with microembolization in patients with symptomatic ICA stenosis[36] and neutrophil number within the plaque is associated with histopathologic features of rupture-prone atherosclerotic lesions.[37] Given their potential role in plaque destabilization, it is not surprising that a high NLR was associated with symptomatic ICA stenosis. Lymphopenia, which mainly results from increased apoptosis of lymphocytes associated with their redistribution within the lymphatic system, is a common feature of inflammatory process.[38] Lymphopenia reflects a generalized state of immunodepression and has been identified as a predictor of mortality in several cardiovascular diseases including coronary heart disease and advanced heart failure.[10,39,40] In our cohort, patients with NLR > 2.95 had significantly higher neutrophil and lower lymphocyte count. Both factors reflect inflammatory process and may potentially play a role in plaque remodeling and thus

Table 2. *Comparison of patients'' characteristics according to the PLR value*

Characteristics		Group Ib PLR < 86.6 (n = 68)	Group IIb 86.6 < PLR < 111.7 (n = 67)	Group IIIb 111.7 < PLR < 148.3 (n = 68)	Group IVb PLR > 148.3 (n = 67)	*P* value
General characteristics	Age	67.9 ±10.1	74.5 ±9.4	72.4 ±9.8	75.60±9.20	<0.0001
	Male sex	47 (69.1%)	41 (61.2%)	43 (63.2%)	47 (70.10%)	0.631
	Diabetes	21 (30.9%)	17 (25.4%)	16 (23.5%)	18 (26.90%)	0.797
	Arterial hypertension	47 (69.1%)	52 (77.6%)	47 (69.1%)	51 (76.10%)	0.554
	Dyslipidemia	28 (41.2%)	25 (37.3%)	27 (39.7%)	19 (28.40%)	0.412
	Smoking	32 (47.1%)	14 (20.9%)	19 (27.9%)	13 (19.40%)	0.001
	Atrial fibrillation	8 (11.8%)	5 (7.5%)	5 (7.4%)	6 (9%)	0.787
Clinical characteristics	Symptomatic ICA stenosis	32 (47.1%)	24 (35.8%)	31 (45.6%)	40 (59.70%)	0.051
	Degree of ICA stenosis (%)	74.9 ±10.9	75.4 ±9.8	74.8 ±9.9	74.30±10.50	0.948
Procedural characteristics	Carotid clamping time (min)	37.3 ±15.6	42.4 ±13.6	36.1 ±13.8	33.40±13	0.006
	Shunt	7 (10.3%)	2 (3%)	5 (7.4%)	3 (4.50%)	0.309
	Surgical technique	39 (57.4%)	46 (68.7%)	41 (60.3%)	32 (47.80%)	0.104
	Patch	28 (41.2%)	21 (31.3%)	27 (39.7%)	35 (52.20%)	0.106
	Eversion	1 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0.395
	Bypass	8.4 ±2.1	7.9 ±2.5	7.3 ±2	8.30±2.80	0.051
Blood count	Leukocytes (*10^9 /L)	4.4 ±1.5	4.8 ±2.3	4.4 ±1.6	5.80±2.70	<0.0001
	Neutrophils (*10^9 /L)	3 ±0.8	2.6 ±0.5	2 ±0.6	1.40±0.40	<0.0001
	Lymphocytes (*10^9 /L)	0.8 ±1	0.8 ±1	0.6 ±0.2	0.80±0.30	0.335
	Monocytes (*10^9 /L)	209.5 ±55	224.4 ±53	245.2 ±71.8	280.30±86	<0.0001
	Platelets (*10^9 /L)	14 ±1.9	13.7 ±1.5	14 ±1.5	13 ±1.90	0.002
	Hemoglobin (g/dL)	71.5 ±12.3	99.8 ±7.5	125.2 ±10.6	207.30±52.10	<0.0001
	PLR	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)	0.386
30-day postoperative outcome	Mortality	8 (11.8%)	11 (16.4%)	8 (11.8%)	7 (10.40%)	0.740
	All-cause complications	0 (0%)	8 (11.9%)	3 (4.4%)	1 (1.50%)	0.004
	Neurologic complications	0 (0%)	2 (3%)	0 (0%)	0 (0%)	0.107
	TIA	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)	0.385
	Ischemic stroke	0 (0%)	1 (1.5%)	0 (0%)	0 (0%)	0.385
	Hemorrhagic stroke	0 (0%)	4 (6%)	3 (4.4%)	1 (1.50%)	0.159
	Cranial nerve injury/ seizure	5 (7.4%)	2 (3%)	2 (2.9%)	2 (3%)	0.475
	Vascular complications	1 (1.5%)	1 (1.5%)	1 (1.5%)	3 (4.50%)	0.555
	Cardiac complications					

Values are mean ±standard deviation or n (%). % are expressed compared to the groups (67- 68 patients).
Abbreviations: ICA, internal carotid artery; NA, not applicable; PLR, platelet to lymphocyte ratio.

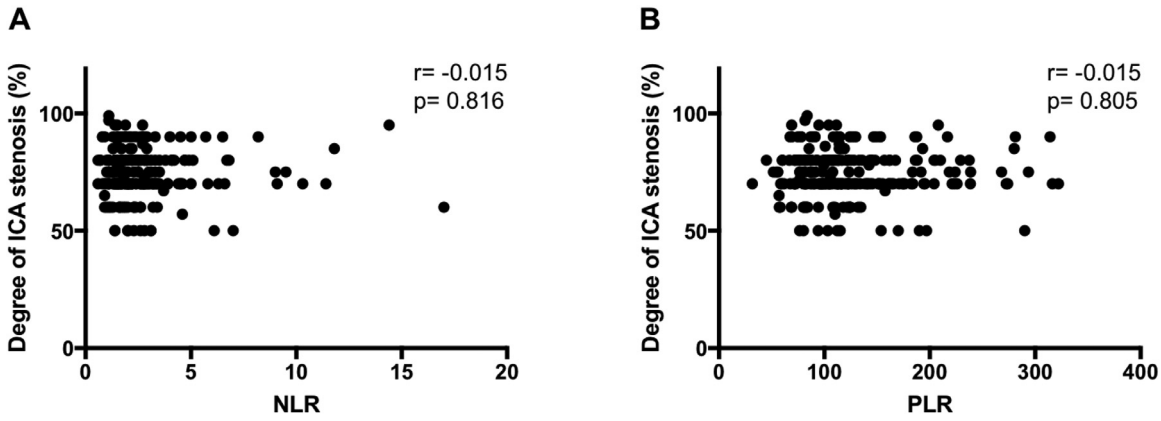

Figure 1. *Correlation between the severity of ICA stenosis and white blood count ratio. (A) Correlation between the degree of ICA stenosis and NLR. (B) Correlation between the degree of ICA stenosis and PLR. Abbreviations: ICA, internal carotid artery; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio.*

may be involved in the association observed between NLR and symptomatic ICA stenosis. It has also been hypothesized that NLR reflects the relative activity of the autonomic system, neutrophils being stimulated by the sympathetic nerves and lymphocytes by the parasympathetic system.[41] As the dysregulation of the autonomic nervous system impacts on atherosclerosis pathogenesis,[42] it could be a potential mechanism linking the NLR with symptomatic ICA stenosis.

The significance of PLR in context of ICA stenosis has been less investigated. Published studies highlighted a correlation between the PLR and the severity of ICA stenosis. The PLR was higher in patients with critical ICA stenosis (including symptomatic ICA stenosis>50% and asymptomatic ICA stenosis >80%) compared with the noncritical group.[43] In addition, the PLR was positively correlated with the degree of ICA stenosis and was an independent predictor of stroke.[18] Even if we did not identify a direct correlation between the PLR and the degree of ICA stenosis, a high PLR was significantly associated with symptomatic ICA stenosis, suggesting a relationship between the PLR and the clinical consequences of ICA stenosis. Platelets play a role in the initiation and progression of atherosclerotic lesions through their involvement in hemostasis and their ability to secrete inflammatory mediators that regulate the chemotaxis of immune cells.[44,45] A high platelet count is associated with poor prognosis and higher mortality among patients with coronary artery disease and platelets impact on plaque stability.[46,47]

In this study, we did not observe any significant difference on 30-day postoperative all-cause complications when the population was divided according to the preoperative NLR and PLR values. The predictive value of the NLR in context of carotid artery surgery has been so far poorly investigated. In a cohort of 432 patients, some investigators found that patients who had cognitive dysfunction at 1 day following carotid endarterectomy had significantly higher NLR compared to those without cognitive dysfunction.[48] Further studies are required to fully determine the potential predictive value of the NLR and the PLR on postoperative outcomes. In our cohort, we found that patients with a PLR between 86.6 and 111.7 had a higher rate of neurologic complications, and more specifically a higher rate of stroke and transient ischemic attack compared to the other groups. However, the mean carotid clamping time was significantly higher in this group, which may explain the results. At last, patients with high NLR and high PLR were significantly older when compared to the other groups. This is in accordance with a study which demonstrated in the general population that these parameters increase with age.[49]

While the NLR and PLR did not correlate with the 30-day postoperative risk, they were significantly associated with symptomatic carotid stenosis. There is currently a lack of consensus to choose between intensive medical therapy and surgical intervention for patients with asymptomatic carotid stenosis.[50,51] The validation of clinical, radiological, or biological criteria to identify patients at high risk for developing symptoms is urgently needed to help to choose the most appropriate approach. As high NLR and PLR are significantly associated with symptomatic carotid stenosis, they could potentially represent useful biomarkers in this indication.

This study has several limitations and perspectives can be suggested. This was a single-center study with retrospectively collected data. It would be worth extending this study to other centers and to include prospectively patients to better assess the predictive value of the NLR and the PLR on postoperative outcome and on a longer follow-up period.

Conclusions

A high preoperative NLR and PLR is significantly associated with symptomatic ICA stenosis, suggesting the

interest of these markers to assess the severity of the disease. Further studies are required to determine the precise role of these parameters in plaque initiation and progression and to determine their interest as predictor of postoperative outcomes in patients undergoing carotid endarterectomy.

Author Contribution

All authors confirm they contributed to the intellectual content of this article including conception and design. They revised the manuscript and approved the final version.

Acknowledgments

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Conflicts of Interest

None declared.

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