Clinical research

Neutrophil to lymphocyte ratio and platelet to lymphocyte ratio are associated with cryptogenic stroke in patients with patent foramen ovale

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Abstract

Introduction: Although most ischaemic strokes are due to cardioembolism, about 25–40% of strokes are cryptogenic. Patent foramen ovale has been associated with cryptogenic stroke; however, the precise mechanism of this association has not been demonstrated. The aim of this study was to evaluate the association between inflammatory markers and cryptogenic stroke in patients with patent foramen ovale.
Material and methods: We included 206 patients with patent foramen ovale. Ninety-four (45.63%) out of 206 patients had had stroke, and 112 (54.37%) had not had stroke. The ratio of the total neutrophil count to the total lymphocyte count was defined as the neutrophil to lymphocyte ratio, and the ratio of the absolute platelet count to the absolute lymphocyte count was determined as the platelet to lymphocyte count.
Results: The neutrophil to lymphocyte ratio was significantly higher in patients who had stroke than in those who did not (2.41 ±1.69 vs. 2.19 ±1.74, p = 0.047). Although the platelet to lymphocyte count was also higher in patients who had had stroke than in those who had not, it was not statistically significant (120.94 ±55.45 vs. 118.01 ±52.21, p = 0.729). 1.62 was the cut-off value for neutrophil to lymphocyte ratio to be associated with stroke with 73.4% sensitivity and 45.05% specificity (p = 0.042).
Conclusions: This study demonstrated that elevated neutrophil to lymphocyte ratio and platelet to lymphocyte count could be associated with cryptogenic stroke in patients with patent foramen ovale.

Key words: neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, stroke, patent foramen ovale.

Introduction

Stroke is one of the most important causes of mortality and morbidity worldwide [1]. The percentage of ischaemic stroke is the highest among all stroke types, which is more than 80% [2]. Although most ischaemic strokes are due to cardioembolism, about 25–40% of strokes are cryptogenic [3, 4]. Patent foramen ovale (PFO) has been associated with cryptogenic stroke; however, the precise mechanism of this association has not been demonstrated [5, 6]. The prevalence of PFO was shown to be higher in patients with cryptogenic stroke than in the general population [6]. Moreover, some randomised, controlled trials demonstrated a decreased stroke recurrence risk after PFO closure, although such an association has not been confirmed with meta-analysis [5–7].

It has been postulated that inflammation plays a crucial role in all stages of stroke [8]. Chemokines and cytokines released from ischaemic brain tissue attract leukocytes from peripheral blood [8]. Neutrophils are the main leucocytes that aggravate brain injury during ischaemia [9]. It has been found that higher neutrophil levels are associated with larger infarct sizes and more severe strokes [10]. On the other hand, lymphocytes, which are also a part of the inflammatory response, which supress and control the exacerbated inflammatory process, are decreased in peripheral blood of patients with stroke [11]. Hence, the neutrophil to lymphocyte ratio (NLR) is suggested as an inflammation marker of stroke [12]. Similarly, platelet activation contributes to the inflammation, and consequently relative thrombocytosis and initiation and progression of atherosclerosis [12, 13]. Recent studies have demonstrated higher platelet to lymphocyte (PLR) values in patients with stroke [14].

High NLR, PLR, and PFO are known to be independent contributing factors for stroke development, but their additive role in cryptogenic stroke has not been fully investigated. The aim of this study was to evaluate whether NLR and PLR predispose to cryptogenic stroke in patients with PFO.

Material and methods

Study population

We included 206 consecutive patients with PFO in this prospective study. The presence of PFO was demonstrated by transoesophageal echocardiogram (TEE) in all subjects. Ninety-four of these patients were referred to the TEE laboratory from various neurology clinics with the diagnosis of acute ischaemic cryptogenic stroke. Stroke was defined as sudden onset of global or cerebral dysfunction persisting for more than 24 h. All the patients underwent workup for the determination of the source of the embolism leading to stroke, and the ascending aorta, aortic arch, carotid, and vertebral arteries were thoroughly investigated.

A total of 112 healthy controls were referred to the TEE laboratory with suspicion of PFO. Subjects with coronary artery disease, carotid and/or aortic atherosclerotic disease, congestive heart failure, valvular heart disease, paroxysmal atrial fibrillation or any kind of arrythmia, malignancy, chronic obstructive lung disease, complicated diabetes, renal failure, liver failure, major rheumatic diseases, active inflammatory diseases, non-cryptogenic stroke, haemorrhagic stroke, surgery, or trauma within the preceding three months and those with missing laboratory data were excluded. Additionally, patients with signs and symptoms of any kind of recent infection were also excluded because leucocytes, neutrophils, and lymphocytes are elevated during the course of an infection.

Ethics

This study was conducted in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects. Study protocol was explained in detail to the patients and their relatives, and a written, informed consent form was obtained from all study participants. The study was approved by the Intuitional Ethics Committee (No. 2017-17-28).

Blood analysis

Complete blood cell counts, including total white blood cells (WBC), neutrophils, lymphocytes, and platelets, were obtained at the time of admission to the TEE laboratory in all subjects. The time window for blood sampling was more than 48 h to less than one week in patients with stroke. The NLR and the PLR were calculated as neutrophil count divided by lymphocyte count, and platelet count divided by lymphocyte count, respectively.

Assessment of TEE

All patients underwent complete two-dimensional TEE with an echocardiography device (EpIQ 7C, Philips Healthcare) operated by a single experienced cardiologist. Data acquisition was performed with a 7 MHz transducer. Mid-oesophageal long-axis view was used for PFO recognition. TEE parameters were recorded according to the recent related guidelines of the American Society of Echocardiography [15].

Statistical analysis

MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013) computer software was used for statistical analysis. Normal distribution of continuous variables was analysed by Shapiro-Wilk

test. Normally distributed numeric variables were compared using Student's *t*-test, and non-normally distributed variables were analysed using the Kruskal-Wallis test. Spearman's rank test was employed to analyse correlations among numeric variables. Binary logistic regression test was employed to analyse correlations among categorical variables, and odds ratio and 95% confidence intervals were calculated. The NLR and PLR were evaluated by comparing the areas under the receiver operating characteristic curve (AUC) in predicting the patients with PFO and stroke. The linear correlations were evaluated to determine the relationship between lymphocyte counts, NLR, PLR, and stroke. Statistical significance was accepted as $p < 0.05$.

Results

The demographic features and laboratory findings of the patients are presented in Table I. Laboratory findings are presented in Table II. Accordingly, haemogram and haemotocrit values were higher in patients with stroke than in healthy individuals (13.98 ±1.57 vs. 13.51 ±1.6, $p = 0.012$ and 42.17 ±4.2 vs. 41.04 ±4.1, $p = 0.017$, respectively). Neutrophil count was also higher in the stroke group than in the healthy group (5.24 ±2.56 vs. 4.46 ±1.87, $p = 0.004$). PLR was not significantly different between the groups (120.94 ±55.45 vs. 118.01 ±52.21, $p = 0.72$). NLR was significantly higher in the stroke group than in the control group (2.41 ±1.69 vs. 2.19 ±1.74, $p = 0.047$). ROC analysis for NLR and PLR is presented in Table III. Accordingly, 1.62 was the cut-off value for NLR to be associated with stroke, with 73.4% sensitivity and 45.05% specificity ($p = 0.042$) (Figure 1). 96.21 was the cut-off value for PLR, with 70.21% sensitivity and 39.29% specificity ($p = 0.729$) (Figure 2). Correlation analysis revealed that NLR was

Table I. Demographic features of the patients in groups

Parameter	Control group *n* (%)	Stroke group *n* (%)	*P*-value
Gender	65 (58.04)	33 (35.11)	0.001
Hypertension	63 (56.25)	43 (45.74)	0.162
Diabetes mellitus	52 (46.43)	49 (52.13)	0.484
Hyperlipidaemia	54 (48.21)	42 (44.68)	0.675
Family history	49 (43.75)	45 (47.87)	0.577
Smoking	67 (59.82)	54 (57.45)	0.777

Table II. Laboratory findings and ages of the patients in the groups

Parameter	Control group Mean ± SD Med. (min.–max.)	Stroke group Mean ± SD Med. (min.–max.)	*P*-value
Haemogram	13.51 ±1.6 13.3 (10–17.9)	13.98 ±1.57 14.1 (9.65–17.3)	0.012
Haematocrit	41.04 ±4.1 40.56 (29.4–50.6)	42.17 ±4.2 42.8 (30.8–51.7)	0.017
Lymphocyte	2.39 ±0.83 2.25 (0.65–5.39)	2.41 ±0.63 2.36 (0.65–3.84)	0.364
Leucocyte	7.65 ±2.12 7.53 (3.94–14.7)	8.56 ±2.68 7.9 (4.47–22.19)	0.005
Platelet	255.46 ±67.33 246.5 (91–522)	268.7 ±64 260 (117–486)	0.098
Platelet/lymphocyte	118.01 ±52.21 108.49 (41.17–411.82)	120.94 ±55.45 111.62 (56.4–466.15)	0.729
Leucocyte/lymphocyte	3.55 ±1.85 3.08 (1.72–16.53)	3.83 ±2.05 3.25 (2.14–14.2)	0.065
Neutrophil	4.46 ±1.87 4 (1.48–12.09)	5.24 ±2.56 4.67 (1.88–19.14)	0.004
Neutrophil/lymphocyte	2.19 ±1.74 1.72 (0.5–14.73)	2.41 ±1.69 1.91 (0.9–11.84)	0.042
Age	39.98 ±15.81 37 (17–79)	51.19 ±11.81 51 (17–79)	< 0.001

Table III. Receiver operating characteristics (ROC) curve analysis of neutrophil/lymphocyte and platelet/lymphocyte ratios

Stroke group vs. control group	AUC	*P*-value	Cut-off	Sensitivity	95% Lower CI	95% Upper CI	Specificity	95% Lower CI	95% Upper CI
NLR	0.581	0.042	1.62	73.40	63.3	82.0	45.05	35.6	54.8
PLR	0.514	0.729	96.21	70.21	59.9	79.2	39.29	30.2	49.0

NLR – neutrophil/lymphocyte, PLR – platelet/lymphocyte.

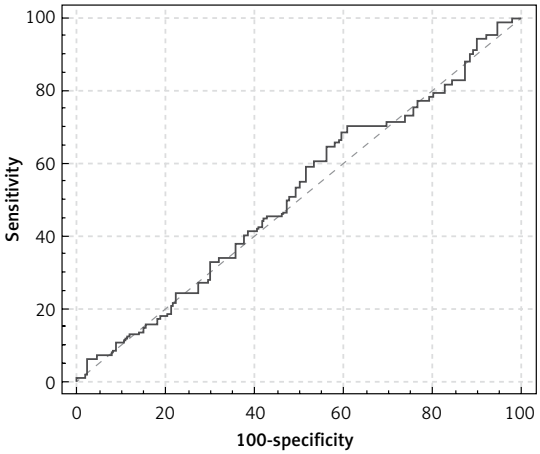

Figure 1. Receiver operating characteristics (ROC) curve analysis revealed that the PLR ≥ 96.21 was predictive of stroke in patients with PFO with sensitivity 70.21%, specificity 39.39%, $p = 0.729$

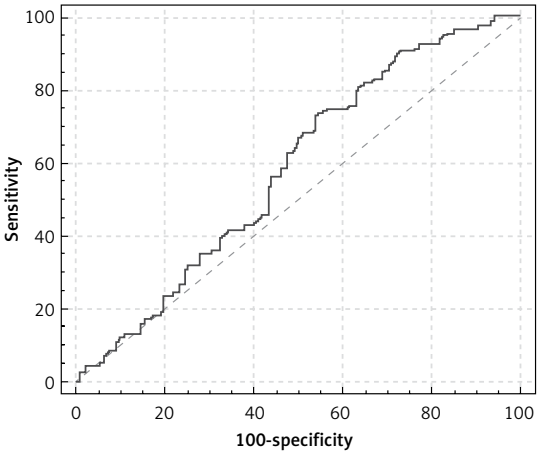

Figure 2. Receiver operating characteristics (ROC) curve analysis revealed that the NLR ≥ 1.62 was predictive of stroke in patients with PFO with sensitivity 73.4%, specificity 45.5%, $p = 0.042$

positively correlated with leucocyte count ($p < 0.001$) (Table IV). There was a negative correlation between PLR and haemogram and haematocrit levels, and a positive correlation between PLR and neutrophil ($p = 0.006$, $p = 0.011$, and $p < 0.001$, respectively) (Table IV).

Table IV. Correlation analysis of neutrophil/lymphocyte and platelet/lymphocyte ratio

Parameter		NLR	PLR
Haemogram	*r*	–0.075	–0.190
	p	0.288	0.006
Haematocrit	*r*	–0.112	–0.178
	p	0.109	0.011
Lymphocyte	*r*	–0.610	–0.683
	p	< 0.001	< 0.001
Leucocyte	*r*	0.368	–0.120
	p	< 0.001	0.085
Platelet	*r*	–0.038	0.452
	p	0.585	< 0.001
Leucocyte/ lymphocyte	*r*	0.972	0.580
	p	< 0.001	< 0.001
Neutrophil	*r*	0.733	0.143
	p	< 0.001	0.041
Age	*r*	0.106	0.021
	p	0.130	0.761

NLR – neutrophil/lymphocyte, PLR – platelet/lymphocyte.

Discussion

Our study demonstrated that the NLR of stroke patients with PFO was higher than those without stroke. Also, PLR was elevated in the patient group compared to controls, but this was not statistically significant. To the best of our knowledge, this is the first study that has evaluated the association between these inflammatory markers and stroke risk in patients with PFO. Moreover, 1.62 was determined to be the cut-off value for NLR to predict stroke in patients with PFO; however, the sensitivity and especially the specificity of this cut-off value were low (73.4 % sensitivity and 45.05% specificity).

The literature includes studies regarding the development of stroke in various disease settings such as prostate [16] and breast cancer [17]. However, as a cardiac disorder, estimation of development of ischaemic stroke is especially clinically important for patients with PFO, where PFO closure, although still controversial, is an option

that may preclude worse outcome [5, 18]. Local intraseptal thrombosis and paradoxical embolism are proposed as the main mechanisms of stroke in patients with PFO [6]. However, the existence of PFO seems not to be the exclusive reason for stroke [5]. Other parameters such as the morphology of PFO, presence of septal aneurysm, and deep venous thrombosis are sought before PFO closure to reduce recurrent stroke risk [5, 6]. Inflammation is related with an increased risk of thrombosis [13, 19]. To date, the association between NLR and PLR, which are markers of inflammation, atherosclerosis, and stroke, have not been evaluated in patients with PFO. Our study is the first to demonstrate such a relationship.

Recent research has revealed that haematological markers such as NLR and PLR are more powerful inflammatory biomarkers than total WBC count in many diseases including stroke, atrial fibrillation, and myocardial infarction [20, 21]. The neutrophil/lymphocyte ratio (NLR) has been shown to predict cardiovascular events in several studies [22]. Shah *et al.* demonstrated that elevated NLR in healthy subjects is a risk factor for increased prospective cardiovascular mortality [23]. Suh *et al.* indicated increased prospective ischaemic stroke risk among asymptomatic patients who had elevated NLR [22]. Also, other relevant studies suggested the addition of NLR to traditional stroke and cardiovascular disease risk prediction models [22]. Moreover, the prognostic significance of these markers has also been demonstrated in various diseases such as stroke, heart failure, and peripheral arterial occlusive disease [12, 24, 25]. For instance, Fang *et al.* showed that the NLR significantly and independently predicted in-hospital mortality in patients who had ischaemic stroke [24]. Similarly, Tokgoz *et al.* and Celikbilek *et al.* also found similar correlation between clinical outcome and NLR in patients hospitalised with stroke [26, 27]. Additionally, high NLR has been assessed in venous thrombosis [28]. The investigators of the Tromso study indicated a correlation between elevated NLR and mortality risk among patients with venous thromboembolism [28].

Similarly to NLR, PLR is an easy-to-obtain, inexpensive blood test reflecting platelet reactivity [14]. Previous studies have demonstrated that PLR and NLR are feasible markers associated with thrombotic disorders [29, 30]. Ming *et al.* demonstrated increased NLR and PLR among patients with unprovoked acute deep vein thrombosis and highlighted the potential diagnostic value of these markers in venous thrombosis [31]. Furthermore, Ozcan Cetin *et al.* showed the prognostic potential of PLR in their study, which indicated an association between high PLR and in-hospital mortality and long-term adverse events in the setting of acute pulmonary embolism [32]. Artoni *et al.* found increased risk of provoked cerebral vein thrombosis in patients with high PLR values [33]. The importance of PLR in atherosclerosis has also been investigated [34]. Maimaiti *et al.* demonstrated elevated PLR as a marker for both predicting insufficient coronary reperfusion after myocardial infarction and for development of in-hospital adverse events [34]. Altintas *et al.* claimed that an increase in PLR values was associated with aggravating inflammatory process, which led to silent brain infarcts in patients with paroxysmal atrial fibrillation [35].

The single-centred design and small sample size are the major limitations that might have reduced the power of the study. The sensitivity and specificity of NLR and PLR were low in predicting stroke due to the increased range of NLR and PLR levels and the small sample size. Also, this was an observational and nonrandomised study; hence, further randomised studies to evaluate the role of NLR and PLR on PFO and stroke are warranted. As a last limitation, we only measured the haematological markers once, but a serial measurement of the parameters during follow-up might increase the power of the predictions of the studies.

In conclusion, while NLR was significantly higher, PLR was not significantly higher in patients with PFO who had stroke when compared with healthy individuals. The results of our study suggest that these markers may be associated with risk of ischaemic stroke in patients with PFO. Further large-scale studies are warranted to evaluate the incremental value of NLR and PLR in order to predict the development of ischaemic stroke in patients with PFO.

Conflict of interest

The authors declare no conflict of interest.

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