

# Mean platelet volume and mean platelet volume/platelet count ratio in nonvalvular atrial fibrillation stroke and large artery atherosclerosis stroke

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# Abstract

**Objective** Ischemic stroke subtypes such as patients with large artery atherosclerosis, cardioembolism and embolic stroke of undetermined source were investigated. This study was performed aimed to determine mean platelet volume (MPV) and mean platelet volume/platelet count (MPV/Plt) Ratio in nonvalvular atrial fibrillation (AF) stroke and large artery atherosclerosis (LAA) stroke. **Methods** We conducted a retrospective study of consecutive patients for treatment of acute ischemic stroke at Ruian People's Hospital from March 2017 to October 2018. The patients with ischemic stroke caused by AF and LAA were recruited to this study. Ischemic stroke was confirmed by MRI and MRA, ischemic lesions on diffusion-weighted imaging were measured in terms of size, composition, and pattern. MPV and platelet count were examined and (MPV/Plt) Ratio was calculated. **Results** 371 patients were enrolled composing of 177 (47.7%) nonvalvular AF and 194 (52.2%) with LAA. The MPV ( $11.3 \pm 1.3$  vs.  $10.8 \pm 1.0$ ,  $p < 0.001$ ) and MPV/Plt ratio ( $0.066 \pm 0.025$  vs.  $0.055 \pm 0.020$ ,  $p < 0.001$ ) were much higher in AF group than LAA group. ROC analysis showed MPV (AUC: 0.624, confidence interval: 0.567-0.68,  $p < 0.001$ ) and MPV/Plt (AUC: 0.657, confidence interval: 0.601-0.713,  $p < 0.001$ ) predicted AF between the two groups. MPV/Plt ratio was negatively associated with lesion volume ( $r = -0.161$ ,  $p = 0.033$ ) in AF. The analyses of subtypes of composition of infarcts and infarct pattern showed that MPV/Plt ratio was almost higher in AF than LAA except for subcortical-only pattern. Multivariable regression analyses demonstrated NIHSS score ( $r = 2.74$ ;  $p < 0.001$ ), LAD ( $r = -1.15$ ;  $P = 0.025$ ) and MPV/Plt ratio ( $r = -180.64$ ;  $P = 0.021$ ) were correlated with lesion volume. **Conclusion** Our results indicated elevated MPV and MPV/Plt ratio for the identification of difference between AF and LAA in patients with ischemic stroke.

## Introduction

Ischemic stroke is the most common subtype of stroke and responsible for mortality and severe morbidity. Ischemic stroke is a heterogeneous disease induced by multiple pathologic mechanisms and lead to a disruption of blood flow and brain damage (1). Most ischemic strokes are embolic (2), including cardiogenic embolism, arteriogenic embolism and paradoxical embolism. Large artery atherosclerotic stenosis (LAA) comprises about 25% of ischemic strokes (3). Cardiogenic embolism accounts for 17% to 30% of all ischemic strokes (3), and atrial fibrillation (AF) is the leading cause of cardiogenic embolism. Before, during, or after the initial onset, 11.5% of patients with an ischemic stroke were diagnosed with AF (4).

Embolism formation can be triggered by artery atherosclerotic stenosis. Furthermore, emboli can originate from left atrial appendage due to AF. That the mechanisms of the progression and development of the two subtypes of embolic stroke of determined source are same or different remains unknown. Circulating platelets are heterogeneous in size, density and activity, and play a critical role in the pathological process of thrombus formation (5). Emboli associated with AF are relatively more commonly larger than that associated with LAA, resulting in territorial infarcts (6). Mean platelet volume (MPV) is an important indicator of platelet activity for containing more granule secretions, thromboxane synthesis and expression of glycoprotein IIb/IIIa receptors (7, 8). MPV level reflects platelet size and

activity. Hence, Larger platelets contain more platelet granules and lead to thrombosis at atherosclerotic stenosis. MPV predicts restenosis after coronary and carotid angioplasty (9, 10). Moreover, MPV is also considered as a risk marker of thrombogenesis in atrial fibrillation (11). It has been shown that MPV is positively associated with severity of ischemic strokes (12) and a worse outcome (13). However, platelet count was lower in patients with ischemic stroke and ischemic heart disease compared with control subjects because of the increasing consumption for thrombus formation (14, 15).

Mean Platelet Volume/Platelet count (MPV/Plt) ratio is a new marker and it has reported that predicted 90-day outcome in LAA stroke (16). Recent study showed that a high MPV/Plt ratio is associated with vein-graft occlusion and poor outcomes in the early period after CABG (17). To our best knowledge, the correlations of MPV/Plt ratio with ischemic lesion volume in nonvalvular atrial fibrillation stroke and large artery atherosclerosis stroke have not been well investigated. In our study we sought to determine whether MPV/Plt ratio on admission differs in nonvalvular atrial fibrillation stroke and large artery atherosclerosis stroke.

## Methods

### Study population

Patients admitted to Ruian People's Hospital within symptom onset for the treatment of first-ever ischemic strokes were recruited to this study between March 2017 and October 2018. Patients were eligible for the study if they were admitted within 7 days of stroke onset and exhibited evidence of acute ischemic stroke on MRI and MRA. Patients with 1) extracranial or intracranial atherosclerosis causing  $\geq 50\%$  luminal stenosis or occlusion of arteries supplying the ischemia area, 2) no major-risk cardiogenic embolism by history, electrocardiography, echocardiography and 24 h dynamic electrocardiogram, and 3) no other specific causes of ischemic stroke were placed into the LAA group. Patients with AF were confirmed by electrocardiography and 24 hour dynamic electrocardiogram, the criterion and classification of HF were used according to the European Society of Cardiology (ESC) HF guidelines. And patients with 1) absence of extracranial or intracranial atherosclerosis causing  $\geq 50\%$  luminal stenosis or occlusion of arteries supplying the ischemia area, 2) no other specific causes of ischemic stroke were placed into the AF group, and 3) absence of valvular heart disease.

The exclusion criteria were 1) malignancies, 2) intracerebral hemorrhage, 3) recent acute coronary syndrome, 4) renal or hepatic diseases, 5) autoimmune diseases, and 6) any other concomitant terminal disease. Patients with other causes of stroke such as valvular AF, cardioembolic stroke without AF, undetermined stroke etiology had been excluded from the study. This study conformed to the Declaration of Helsinki and was approved by ethics committee of Wenzhou People's Hospital and Ruian People's Hospital. Written informed consent was obtained from all subjects or their immediate family members.

### Acute ischemic lesion analysis

The MRI and MRA parameters in this study were measured as previous described (18). The ischemic lesions on diffusion-weighted imaging (DWI) were evaluated including size, composition, and distribution. The infarct volume was calculated by ABC/2 (where A is longest dimension in axis x, B is longest perpendicular dimension to axis x (y), and C is total length in z dimension) (19). Two experienced neurologists independently reviewed neuroimages and reported the results. Patients were divided to three infarct composition pattern groups according to pattern of the ischemic lesion(s): 1) small (< 10 mm in diameter) lesions only, 2) mixed small and large lesions, and 3) large lesions only  $\geq 10$  mm in diameter on DWI (20). Patients were also categorized based on topography pattern of ischemic lesion(s): 1) subcortical-only pattern, 2) small cortical-only pattern, and 3) large cortical/corticaldeep pattern (21).

## Baseline Data Collection

Demographic data (age and sex) and history of risk factors (hypertension, diabetes mellitus, congestive heart failure, history of vascular disease, systolic blood pressure; diastolic blood pressure, smoking, and alcohol abuse) were collected at admission via in-person interviews with the patients or their family members. Blood samples of patients were obtained in the next morning of the day of admission. After centrifugation, aliquots of the samples were immediately stored at  $-80^{\circ}\text{C}$  before assay. Routine blood biomarkers, including triglyceride, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), Lipoprotein (a), high-sensitivity C-reactive protein (hs-CRP), fasting blood glucose (FBG), albumin and Creatinine (Cr), were examined using standard detection methods. MPV as well as leukocyte, erythrocyte, and platelet counts were tested by a Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Japan). We collected echocardiographic parameters from all patients according to the current guidelines (22), including left ventricular ejection fraction (LVEF), Left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDd), left ventricular end-systolic diameter (LVESd) and inter-ventricular septal thickness at end diastole (IVSd).

## Statistical analysis

All the data are expressed as mean  $\pm$  SD.  $\chi^2$  was used to examine differences in discrete variables among the groups. Differences in continuous variables were examined by using Mann-Whitney test and Kruskal-Wallis test. In addition, independent factors for ischemic lesion volume were evaluated using linear regression. Adjustment variables in the multivariable regression models were chosen from potential outcome determinants with significant clinical relevance in univariate analysis. Statistical significance was defined as  $p < 0.05$ . Statistical analysis was performed by using SPSS version 20.0.

## Results

A total of 371 patients enrolled in this study, including 177 (47.7%) patients with nonvalvular AF stroke and 194 (52.2%) patients with LAA stroke. Baseline characteristics of the study subjects were shown in Table 1. AF had higher average age ( $p < 0.001$ ) than LAA, but the proportion of male patients was closer to LAA. The prevalence of current smoking ( $p = 0.001$ ), hypertension ( $p = 0.03$ ), diabetes ( $p = 0.006$ ) were higher in LAA than AF while the prevalence of congestive heart failure ( $p < 0.001$ ) and history of vascular disease ( $p < 0.001$ ) in LAA were lower than AF.

AF had higher rates of antiplatelets ( $p < 0.001$ ), warfarin ( $p < 0.001$ ), new oral anticoagulants (NOAC) ( $p < 0.001$ ). Echocardiographic parameters showed that AF had higher LVEF ( $p < 0.001$ ), LAD ( $p < 0.001$ ) and LVEDs ( $p = 0.003$ ) compared with LAA.

National Institutes of Health Stroke Scale (NIHSS) scores ( $7.1 \pm 5.9$  vs.  $3.3 \pm 2.6$ ,  $p < 0.001$ ) and lesion volume ( $29.5 \pm 51.9$  vs.  $6.9 \pm 5.0$ ,  $p < 0.001$ ) were higher and larger in the AF group than LAA group, which AF group suggested a more severe neurologic presentation. LAA composed of large lesions only was higher than AF while AF composed of mixed small and large lesion was higher. AF had high large cortical/cortical-deep, intermediate small cortical-only pattern, and low subcortical-only pattern. LAA had high small cortical-only pattern, intermediate subcortical-only pattern and low large cortical/cortical-deep.

The MPV ( $11.3 \pm 1.3$  vs.  $10.8 \pm 1.0$ ,  $p < 0.001$ ) and MPV/Plt ratio ( $0.066 \pm 0.025$  vs.  $0.055 \pm 0.020$ ,  $p < 0.001$ ) were much higher in AF group than LAA group (Fig. 1). Moreover, ROC analysis showed MPV (AUC: 0.624, confidence interval 0.567-0.68,  $p < 0.001$ ) and MPV/Plt (AUC: 0.657, confidence interval 0.601-0.713,  $p < 0.001$ ) predicted AF between the two groups (Fig. 2). As was shown in Fig. 3, MPV/Plt ratio was negatively associated with lesion volume ( $r = -0.161$ ,  $p = 0.033$ ) in AF (Fig. 3a). However, MPV/Plt ratio was not associated with lesion volume in LAA (Fig. 3b). Furthermore, there was no correlation of MPV with lesion volume in AF and LAA (Fig. 4).

We next investigated the characteristics of acute ischemic lesions in Table 2. Regarding the composition of infarcts, we found MPV/Plt ratio was significantly increased in large lesions only ( $0.068 \pm 0.025$  vs.  $0.056 \pm 0.021$ ,  $p < 0.001$ ) and small and large lesions, mixed ( $0.064 \pm 0.024$  vs.  $0.052 \pm 0.017$ ,  $p < 0.001$ ) in AF group. Regarding infarct pattern, small cortical-only pattern ( $0.070 \pm 0.027$  vs.  $0.054 \pm 0.018$ ,  $p < 0.001$ ) and large cortical/cortical-deep ( $0.066 \pm 0.027$  vs.  $0.053 \pm 0.023$ ,  $p = 0.01$ ) had higher MPV/Plt ratio only except for the Subcortical-only pattern in AF group ( $0.061 \pm 0.016$  vs.  $0.064 \pm 0.028$ ,  $p = 0.9$ ).

MPV/Plt ratio ( $r = -0.161$ ;  $P = 0.033$ ) were negatively associated with ischemic lesion volume by linear regression (Table 3). According to the findings, multivariable regression analyses were conducted to determine the associations of the independent factors with lesion volume in AF. The association of NIHSS score ( $r = 2.74$ ;  $p < 0.001$ ), LAD ( $r = -1.15$ ;  $P = 0.025$ ) and MPV/Plt ratio ( $r = -180.64$ ;  $P = 0.021$ ) with lesion volume remained significant after adjustment for possible confounders.

## Discussion

AF and LAA are the main causes of ischemic strokes. Our study demonstrated the clinical characteristics across the two subtypes of ischemic stroke. The proportion of male patients, systolic and diastolic blood pressure in AF was closer to those in LAA. the prevalence of current smoking, hypertension, diabetes were higher in LAA than AF while the prevalence of congestive heart failure and history of vascular disease in LAA were lower than AF. AF had higher rates of antiplatelets, warfarin and new oral anticoagulants (NOAC). the levels of total cholesterol, LDL-C, albumin in LAA were higher than AF, but the levels of triglyceride, hs-CRP and Cr in AF were higher. AF had higher LVEF, LAD and LVEDs. More importantly, AF group had higher NIHSS score and lesion volume compared with the LAA group. The results of our study also indicated MPV and MPV/Plt were increased in AF than LAA. Furthermore, MPV and MPV/Plt predicted AF between the two groups in ROC analyses. MPV/Plt was negatively associated with lesion volume in AF. Subgroup analyses, including composition of infarcts and infarct pattern, showed MPV/Plt in AF group was significantly higher than in LAA group. NIHSS score, LAD and MPV/Plt were identified as the independent factors associated with ischemic lesion volume even after possible confounders.

Many researches had reported the differences across LAA, cardioembolism and embolic stroke of undetermined source (23, 24, 25). AF was determined as a major risk cardiac source and a potential cause of cryptogenic stroke (26, 27, 28). Characteristics of ischemia stroke with AF should be investigated and may differ from LAA. LAA group had the higher prevalence of current smoking, hypertension, diabetes were higher in than AF. Though previous studies has demonstrated that hypertension and diabetes were not associated with stroke recurrence and poor outcome among the subtypes of LAA and cardiac embolism (23,24), Whether prevalence of hypertension and diabetes differ in LAA and AF remain unclear. In a small sample, authors determined that hypertension and diabetes were the most important risk factors in LAA (29). No surprisingly, AF had the higher prevalence of congestive heart failure and history of vascular disease, which are high risk factors for stroke (30). The use rates of antiplatelets, warfarin and NOAC were also higher in AF. For laboratory examination, LAA had higher levels of total cholesterol and LDL-C, indicating the atherosclerosis formation. Left atrial enlargement was positively correlated with the development of AF (31). In this study, AF had higher LAD. LVEF differed in AF and LAA, but the values were within the normal range.

Thromboembolism and atherothrombosis are the leading causes of ischemic stroke. Platelet is activated by plaque rupture, inflammation and other conditions and results in the pathological process of thrombus formation (32). The increased MPV value was associated with hypertension (33), diabetes mellitus (34) and atrial fibrillation (35). MPV on admission predicts Long-Term outcome in acute ST-segment elevation and non-ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention (36, 37). MPV was an independent predictor for 90-day outcomes in stroke patients receiving thrombolysis (38). MPV is higher in patients with ischemia stroke than the control and predict poor outcome (39, 40). MPV is positively associated with severity of ischemic strokes (41). Furthermore, MPV is elevated in acute non-lacunar than lacunar ischemic strokes and is associated with lesion size (Mean platelet volume (MPV) increase during acute non-lacunar ischemic strokes). In addition, MPV levels in patients with acute ischemic stroke with nonvalvular AF were significantly higher than those without (42). In the present study, MPV is higher in AF than LAA and predicted AF across the

two groups. However, there was no association of MPV with lesion volume in both AF and LAA. The results suggest MPV could reflect differences between AF and LAA, but not the association with lesion volume.

MPV/Plt ratio was identified as a new marker and reported that increased MPV/Plt ratio was a better predictor of long-term cardiovascular mortality in patients with acute ST-segment elevation and non-ST-segment elevation myocardial infarction than are MPV and platelet count alone in a recent study (43, 44). The increased MPV/Plt ratio was associated with ischemia stroke after acute myocardial infarction (45). The patients with deep vein thrombosis also have a higher MPV/P ratio compared to the control group (46). The increase of MPV/Plt ratio is positively correlative with high risk of pulmonary embolism (47). MPV/Plt ratio predicted 90-day outcome in Stroke Patients with LAA. In this study, we found MPV/Plt ratio was increased in AF and predicted AF across the two categories. Furthermore, the analyses for subtypes of composition of infarcts and infarct pattern determined that MPV/Plt ratio was higher in AF than LAA except for subcortical-only pattern, which might attribute to small sample of AF group. MPV/Plt ratio was also negatively correlated with lesion volume in AF. Finally, we investigated other independent factors with lesion volume in AF. After adjustment for possible confounders, NIHSS score, LAD and MPV/Plt ratio with lesion volume were still significantly correlated with lesion volume.

## Conclusions

In summary, our data indicate that MPV and MPV/Plt ratio were higher in AF than LAA and predicted AF across the two categories. Furthermore, MPV/Plt ratio was higher subtypes of composition of infarcts and infarct pattern in AF except for subcortical-only pattern. MPV/Plt ratio was significantly associated with lesion volume. Our results emphasize the importance of MPV and MPV/Plt ratio for the identification of ischemic stroke between AF and LAA.

## Limitation

Patients were included within 7 days of stroke onset and MPV was taken on admission, however the time of MPV measurement was not specified. The patients in acute phase of stroke with treatment of antiplatelet or anticoagulation treatment, which affect lesion volume were included in this study. Embolic stroke of cryptogenic source have been not investigated, the characteristics of which may be similar to AF or to LAA. Then it is more likely clarify the mechanisms of ischemia stroke.

## Declarations

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### Disclosures

All authors declare no potential conflicts of interest.

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## Tables

Table 1 Baseline characteristics.

	Atrial fibrillation ( n = 177 )	Large Artery Atherosclerosis ( n = 194 )	P value
<b>Characteristic</b>			
Age (years)	76.1 ± 9.3	68.6 ± 12.1	0.001
Male gender, n (%)	98 (55.4)	120 (61.9)	0.205
Systolic blood pressure	157.0 ± 22.8	161.2 ± 23.4	0.078
Diastolic blood pressure	84.6 ± 14.6	83.8 ± 13.6	0.36
<b>Previous vascular risk factors, n (%)</b>			
Current smoking	39 (22)	75 (38.7)	0.001
Hypertension	146 (82.5)	176 (90.7)	0.03
Diabetes	53 (29.9)	86 (44.3)	0.006
Congestive heart failure	14 (7.9)	0 (0)	0.001
History of vascular disease	36 (20.3)	1 (0.52)	0.001
NIHSS score	7.1 ± 5.9	3.3 ± 2.6	0.001
<b>Medications, n (%)</b>			
Beta-blocker	58 (32.8)	4 (2.1)	0.001
ACEI/ARB	41 (23.2)	45 (23.2)	0.901
Statins	170 (96.0)	190 (98.0)	0.248
Antiplatelets	24 (13.5)	183 (94.3)	0.001
Warfarin	82 (46.3)	0 (0)	0.001
NOAC	48 (27.1)	0 (0)	0.001
<b>Biochemical values</b>			
Total cholesterol (mmol/L)	4.3 ± 1.0	4.7 ± 1.0	0.001
Triglyceride (mmol/L)	1.9 ± 0.9	1.5 ± 1.0	0.001
LDL-C (mmol/L)	2.7 ± 1.0	2.9 ± 0.8	0.008
HDL-C (mmol/L)	1.09 ± 0.2	1.1 ± 0.2	0.885
Lipoprotein (a) (g/L)	1.2 ± 0.2	1.2 ± 0.2	0.347
hs-CRP (mg/L)	13.2 ± 22.6	5.6 ± 16.1	0.001
albumin (g/L)	36.6 ± 4.6	37.8 ± 3.3	0.001
Cr (mmol/L)	81.2 ± 35.1	80 ± 73.4	0.004
FBG (mmol/l)	6.0 ± 2.3	6.0 ± 2.3	0.614
<b>Echocardiographic parameters</b>			
LVEF (%)	59.9 ± 8.4	63.7 ± 8.9	0.001
LAD (mm)	41.2 ± 7.1	35.4 ± 4.7	0.001
LVEDd (mm)	48.6 ± 6.6	48.2 ± 4.9	0.851
LVIDs (mm)	32.8 ± 6.3	30.9 ± 4.7	0.003
IVSd (mm)	9.9 ± 1.8	9.9 ± 1.7	0.83
<b>Size of infarcts</b>			
Lesion volume (ml)	29.5 ± 51.9	6.9 ± 5.0	0.001
<b>Composition of infarcts, n (%)</b>			
Large lesions only	69 (39.9)	131 (67.5)	0.001
Small and large lesions, mixed	108 (61.0)	63 (32.5)	0.001
<b>Infarct pattern, n (%)</b>			
Subcortical-only pattern	35 (19.8)	14 (7.2)	0.001
Small cortical-only pattern	53 (29.9)	158 (81.5)	0.001
Large cortical/cortical-deep	89 (50.3)	22 (11.3)	0.001

Data are presented as mean ± SD, or number or percentage of subjects

NOAC, novel oral anticoagulants; HDL, high-density lipoprotein; LDL, low-density lipoprotein; hs-CRP, high-sensitivity C reactive protein; NIHSS, National Institutes of Health Stroke Scale; FBG: fast blood glucose.

Table 2 Analysis of ischemic lesion characteristics for MPV/Plt in AF and LAA.

	MPV/Plt		P value
	AF (n=177)	LAA (n=194)	
Composition of infarcts			
Large lesions only	0.068±0.025 (69)	0.056±0.021 (131)	0.001
Small and large lesions, mixed	0.064±0.024 (108)	0.052±0.017 (63)	0.001
Infarct pattern			
Subcortical-only pattern	0.061±0.016 (41)	0.064±0.028 (14)	0.9
Small cortical-only pattern	0.070±0.027 (54)	0.054±0.018 (156)	0.001
Large cortical/cortical-deep	0.066±0.027 (82)	0.053±0.023 (24)	0.01

Table 3 analysis of factors associated with ischemic lesion volume.

	Univariate analysis		Multivariable analysis	
	Coefficient	P value	Coefficient	P value
Age (years)	0.056	0.458		
Male gender, n (%)	-0.17	0.024		
Current smoking	-0.01	0.894		
Hypertension	0.008	0.919		
Diabetes	-0.114	0.131		
Congestive heart failure	-0.061	0.42		
History of vascular disease	-0.54	0.473		
Antiplatelets	-9.72		-26.56	0.044
Warfarin	-0.123	0.104	-20.05	0.048
NOAC	-0.111	0.142	-18.02	0.111
NIHSS score	0.47	0.001	2.74	0.001
Total cholesterol (mmol/L)	-0.024	0.746		
Triglyceride (mmol/L)	-0.101	0.183		
LDL-C (mmol/L)	-0.31	0.686		
HDL-C (mmol/L)	0.29	0.703		
hs-CRP (mg/L)	0.153	0.042	0.014	0.93
Cr (mmol/L)	-0.179	0.017		
LAD (mm)	-0.164	0.029	-1.15	0.025
MPV/Plt	-0.161	0.033	-180.64	0.021

Multivariate models were adjusted for Antiplatelets, Warfarin, NOAC, NIHSS score, hs-CRP, LAD. CL: confidence interval.

## Figures

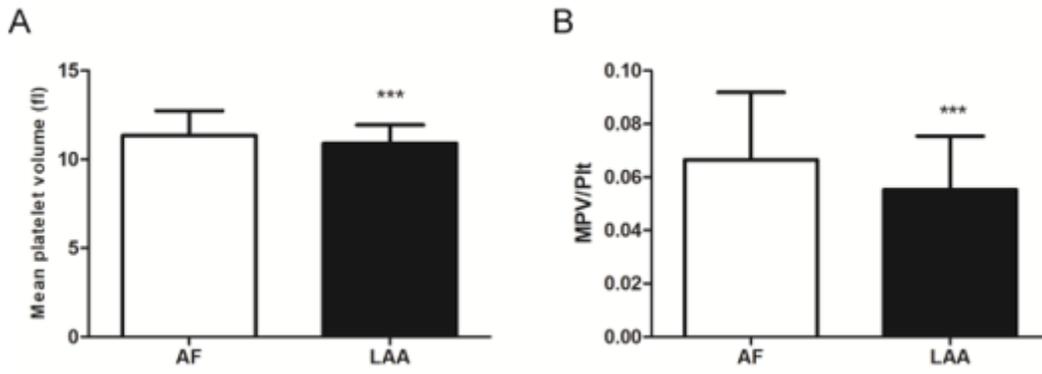


Figure 1

MPV (A) and MPV/Plt (B) in AF and LAA.

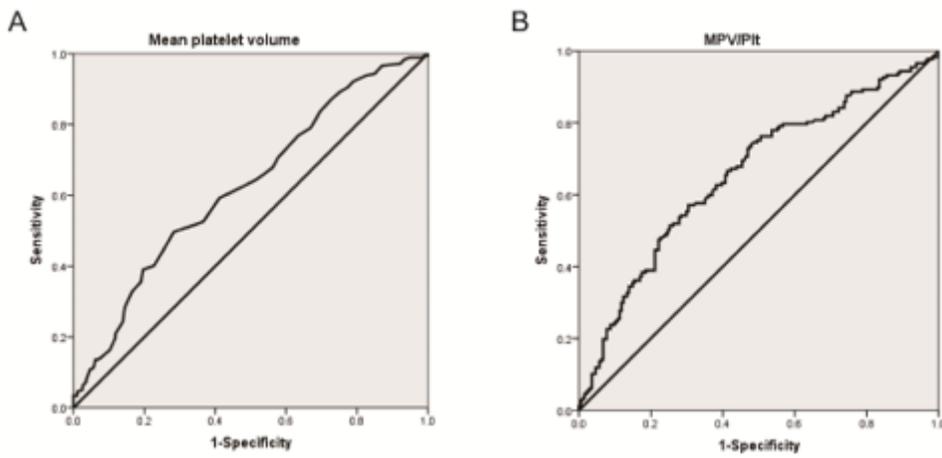


Figure 2

ROC analysis of MPV (A) and MPV/Plt in prediction of AF.

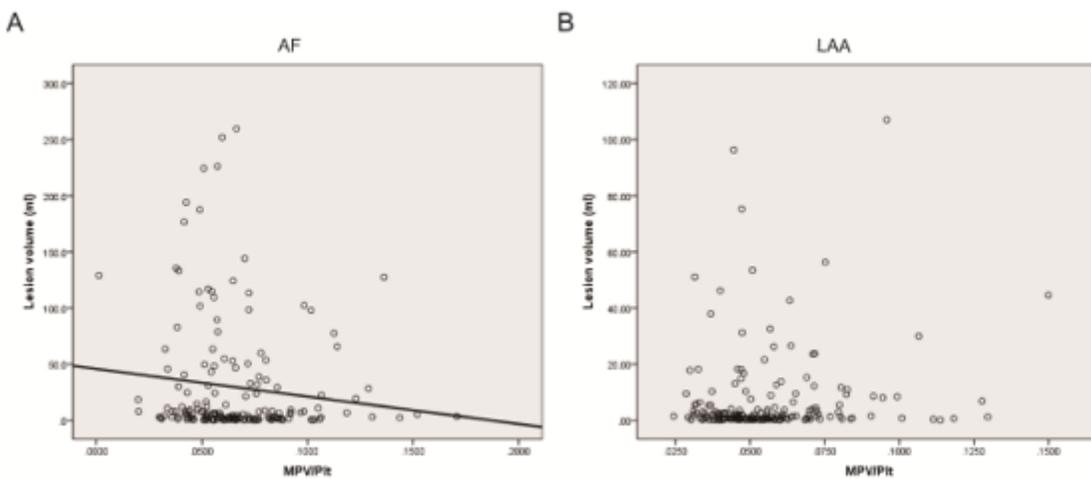
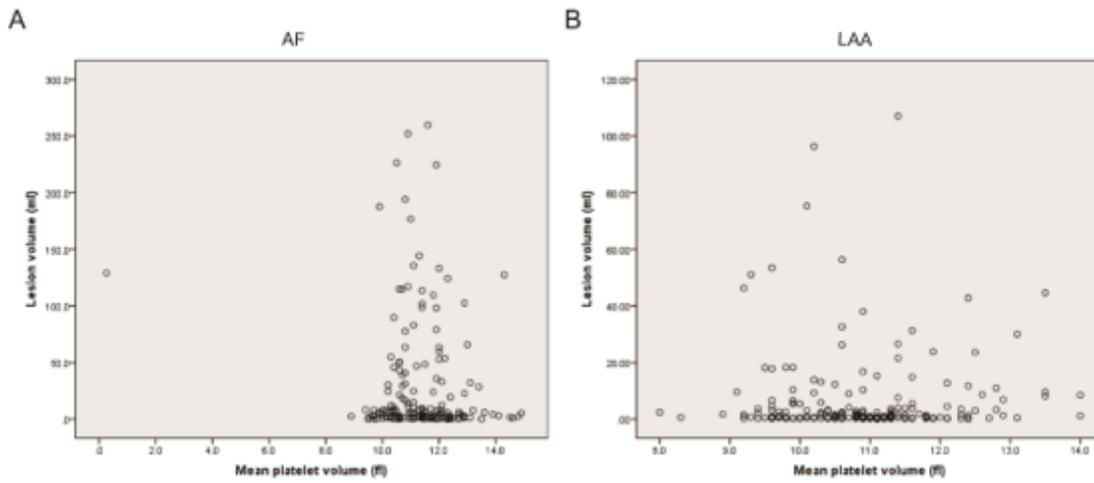


Figure 3

The association of MPV/Plt with lesion volume in AF and LAA.



**Figure 4**

The association of MPV with lesion volume in AF and LAA.